BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

EDITORIAL BOARD

Managing Editor, JAMES BORDLEY, III

E. COWLES ANDRUS
CHARLES R. AUSTRIAN
CHALMERS L. GEMMILL
L. EMMETT HOLT, JR.
ARNOLD R. RICH

VOLUME LXVIII

BALTIMORE
THE JOHNS HOPKINS PRESS
1941

Copyright, 1941
by The Johns Hopkins Press

JAN 22 1941

Medical Library

VOLUME LXVIII

NUMBER 1

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

January, 1941

Eye Movements in the Electroencephalogram. RICHARD S. LYMAN 1

Type I Pneumococcal Pneumonia. JAMES W. HAVILAND, M.D. 32

The Effect of Insulin on Glycogen Deposition and on Glucose Utilization by Isolated Muscles. CHALMERS L. GEMMILL AND LOUIS HAMMAN, JR. 50

Neurotropism and the Genesis of Cerebral Lesions in Poliomyelitis: An Experimental Study. DAVID BODIAN AND HOWARD A. HOWE 58

A Method for the Study of Neuromuscular Transmission in Human Subjects. A. M. HARVEY AND R. L. MASLAND ... 81

Sulfanilylguanidine in the Treatment of Acute Bacillary Dysentery in Children. E. K. MARSHALL, JR., A. CALVIN BRATTON, LYDIA B. EDWARDS AND ETHEL WALKER 94

Proceedings of the Meeting of the Johns Hopkins Medical Society 112

Book Reviews 116

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore, Maryland

Made in United States of America

COPYRIGHT, 1941, BY THE JOHNS HOPKINS PRESS

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, JAMES BORDLEY, III

EDITORIAL BOARD

E. Cowles Andrus — Chalmers L. Gemmill
Charles R. Austrian — L. Emmett Holt, Jr.
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore, Md.

Books of review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.85 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefor adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

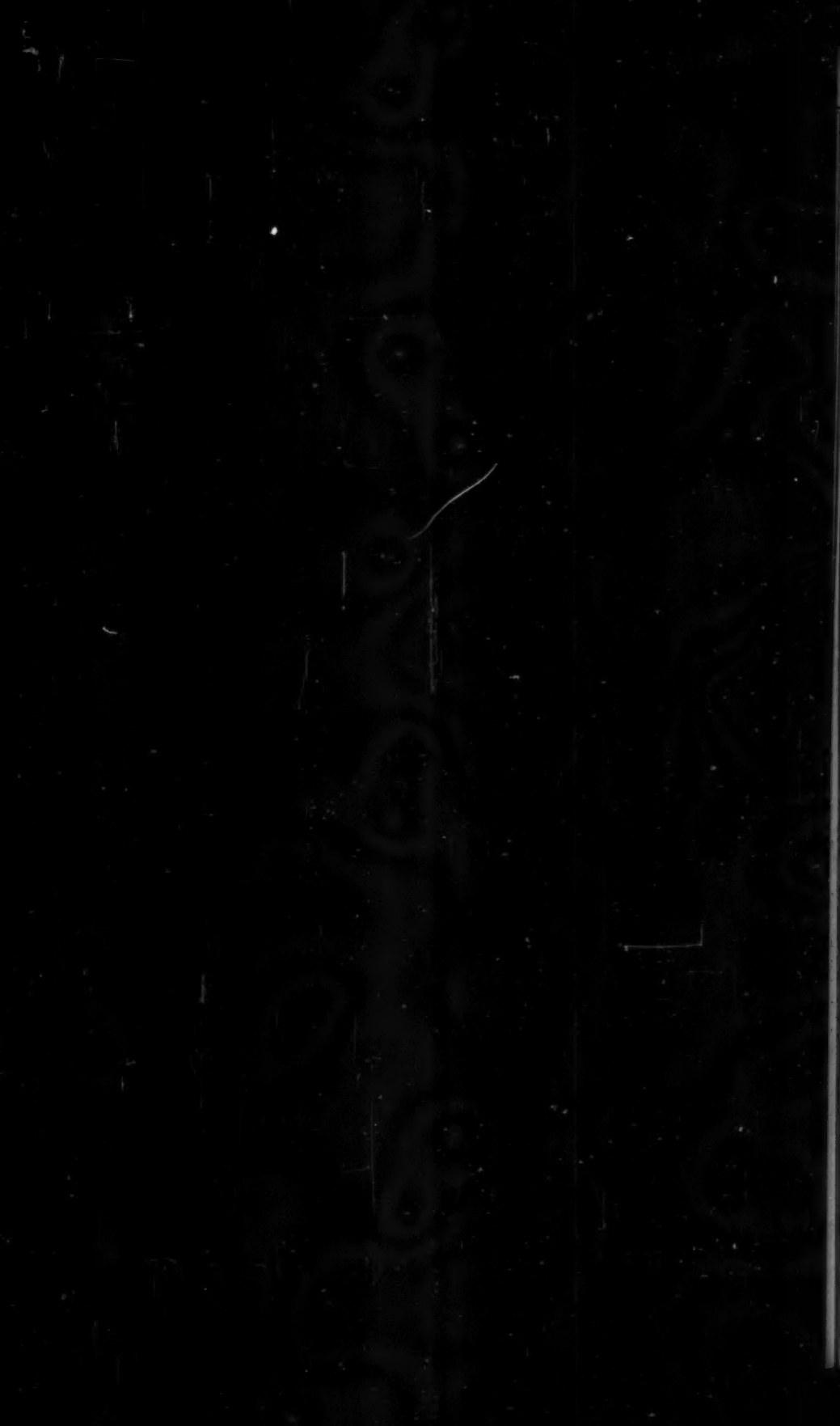
THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

a

—

/



Medical lib.
Fayon

EYE MOVEMENTS IN THE ELECTROENCEPHALOGRAM

RICHARD S. LYMAN

Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital

Submitted for publication September 21, 1940

Electroencephalography inadvertently provides graphic records of eye movements. In interpreting the brain waves it may be common practice also to interpret the eye elements, but rather little has appeared in the electroencephalographic literature about the exact nature and the clinical significance of these eye deflections. They have even been regarded as artefacts because they do not directly represent changes of potential in the cerebral cortex, as pointed out by Jung (7). Failure fully to utilize the eye movements in reading the brain waves may be attributed to the fact that, with the exception of blinks and clear-cut nystagmus, the electroencephalogram in its usual form seldom provides conclusive evidence of any particular sort of eye movement. In fact, the picture presented in the brain waves may be actually misleading.

MAIN LIMITATIONS OF THE USUAL ELECTROENCEPHALOGRAM FOR THE INTERPRETATION OF EYE MOVEMENTS

The records of ocular movement may be distorted by the *position of the electrodes*. This is to be expected when one considers that the positions of the electrodes used for picking up the cortical potentials are far from the eyes and are chosen with reference to the underlying brain and without regard for the directions of the visual axes. By way of demonstration, a normal subject looked alternately from a central spot to other measured spots at the periphery of a circle, while a record was made, using our standard positions of electrodes for brain waves with additional electrodes placed around the eyes, as shown in Fig. 1. A plot of this field of eye movements was made. Samples of the results were then chosen and appear in Fig. 2, to show how normal ocular motility may suggest some paresis, imbalance or even dissociation of action of the extraocular muscles in a record of the brain waves.

FIG. 1. Positions of electrodes and dipolar connections used for recording eye movements, frontal brain waves and frontalis muscular action-potentials.

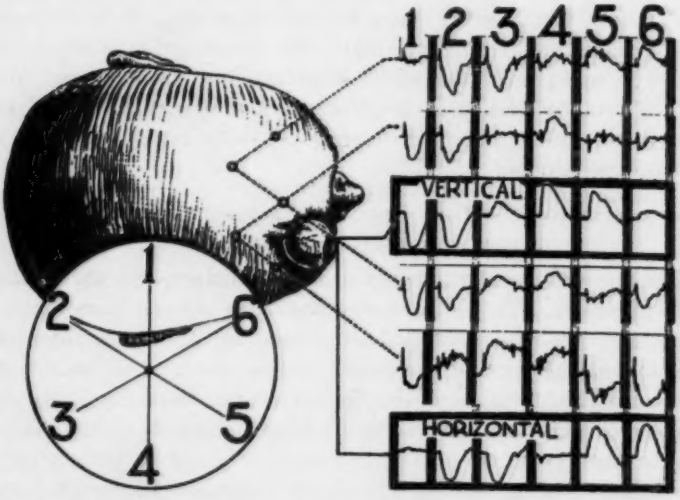


FIG. 2. Distortion of records of eye movements due to position of electrodes. The subject looked from the center of the circle to measured points at the periphery, while registration was made simultaneously from:

a) Electrodes around the right eye, shown in the black-rimmed series, for deviations of the eye in the vertical and horizontal axes, as labelled. These give relatively accurate registration of eye movement.

b) Electrodes on the scalp, with positions and connections as indicated on the diagram. These show considerable distortion in the record of eye movement.

Another limitation lies in the *characteristics of the Grass apparatus*, which is used in electroencephalography here as well as in many other American clinics. If there is a difference of potential, the instrument records the change as a swing which continues back to the base line as soon as the new value has been reached and has become constant. Accordingly, the eyeball might move lateralward, for example, and might stay fixed in motionless lateral deviation. The record would show the lateral movement as a swing which would return to the base line as soon as the eyeball became motionless. There would be nothing in the graph to show that the eyeball had remained in a lateral position and had not returned to central position with the swing of the graph back to the base line. With electrodes around the eyes, a change in the position of the eyeball, whether voluntary or involuntary, would appear in the graph but the exact spacial relationships of the eye to the orbit, or of one eyeball to the other, cannot be read from these deflections in the graphic record.

There are other limitations of less practical importance, which will not be discussed here,—for example, the rather low sensitivity to very slight movement, difficulty in determining rotation of the eyeball especially around the central sagittal axis, and the significance of changes in relationships as soon as the cornea with positive polarization rolls up under the negatively polarized eyelid.

TECHNIQUE OF RECORDING THE EYE MOVEMENTS

To avoid gross distortion due to position of the electrodes, one can put solder or silver electrodes around the eyes. This is very simple, takes little time, requires only small disc-electrodes with electrode paste and adhesive tape, needs only low amplification, and is a procedure which has already been used for the purpose of recording nystagmus graphically (1 to 11). In this clinic, we have recently used this procedure for a somewhat wider purpose in selected cases and have arrived at a semi-standardized scheme. Fig. 1 shows the positions of the electrodes and bipolar connections for recording with a 6-channel Grass electroencephalograph. With relatively low amplification, channel 1 is connected with electrodes placed just lateral to the outer corners of the eyes and it records the horizontal conjugate movements; channel 2 is connected with electrodes just above and

below the left eye; channel 3 with electrodes above and below the right eye, each recording the vertical movements of the corresponding eye separately. With the usual amplification for recording the brain waves, channels 4, 5 and 6 are connected with electrodes placed in an arc across the anterior part of the head, to cover the frontal lobes, which is one of the routine settings adopted here in attempting cerebral localization with the brain waves. The electrodes around the eyes correct a good deal of the distortion due to the position of those on the scalp. Whereas the brain waves alone have often suggested inequalities or dissociation in the eye movements, it has repeatedly been found with the additional electrodes around the eyes that these suspicious irregularities in synchronous timing usually appear to be mere artefacts of position of the scalp electrodes. The part played by each eye in the horizontal conjugative movements can be estimated, if desired, by using the usual mono-di-monopolar system of connections, a common procedure in electroencephalography. Incidentally, the additional electrodes around the eyes also help in determining whether slow deflections in the brain waves from the frontal region are of ocular or cortical origin. The low amplification used in the connections from the eye electrodes does not permit brain waves to come through, except in high-voltage discharges, such as occur in some epileptic attacks. When slow frontal deflections in the brain waves only occur synchronously with those from the eye electrodes, they are regarded as being of ocular origin.

Procedure in Examination of Patients: With or without a simultaneous electroencephalogram, the technical procedure just outlined should give valid records of the movements of the eyes. However, these graphs are likely to have little practical significance unless one knows the condition of the patient at the time. Furthermore, it seems essential to add certain tasks for the patient to perform in order to put the motility of the eyes to test while the records are being made. During the course of the past two years various clinical methods have been tried. A few have finally been retained because of their brevity, simplicity and ready adaptability to the conditions of our brain-wave chamber, where the electroencephalograms are for the most part taken with patients lying on a couch. The procedures consist of spontaneous movements with eyes open and with eyes

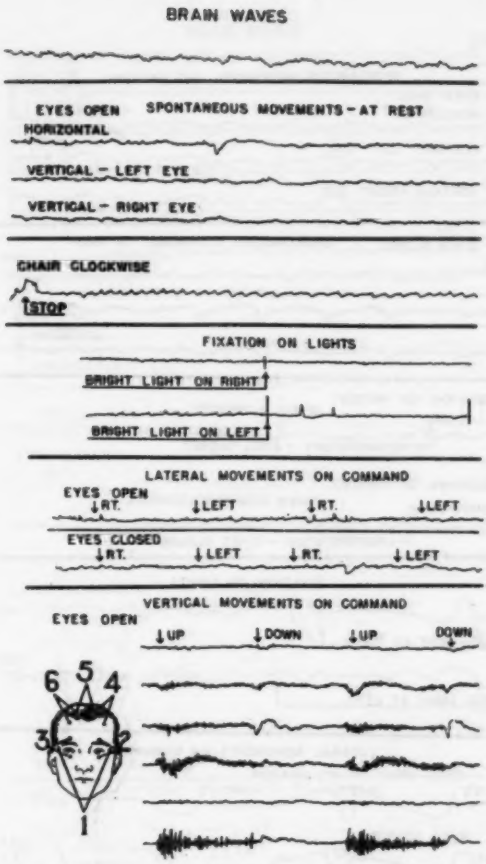


FIG. 3. J. W. C. Blind since birth, due to gonorrheal conjunctivitis, followed by ulceration of the cornea of both eyes and panophthalmitis. The eyes can now be noved only a little and then without good control.

Brain waves from the left occipital region: very poorly formed waves and no recognizable alpha.

Spontaneous movements: minimal with eyes open or closed.

Vestibular stimulation: slight but definite phasic nystagmus in the proper directions.

Fixation on bright lights (which the patient could just make out vaguely): only a few small spikes, indicating minute muscular twitches, but no definite deviation of the eyeballs.

Lateral movements on command: similar small spikes, showing effort, but no actual turning of the eyeballs.

Vertical movements on command: minimal deflections, although there are some few small deflections showing upward movements. The bottom three lines show good frontalis muscular contractions, an associated sign of good effort in looking upward.

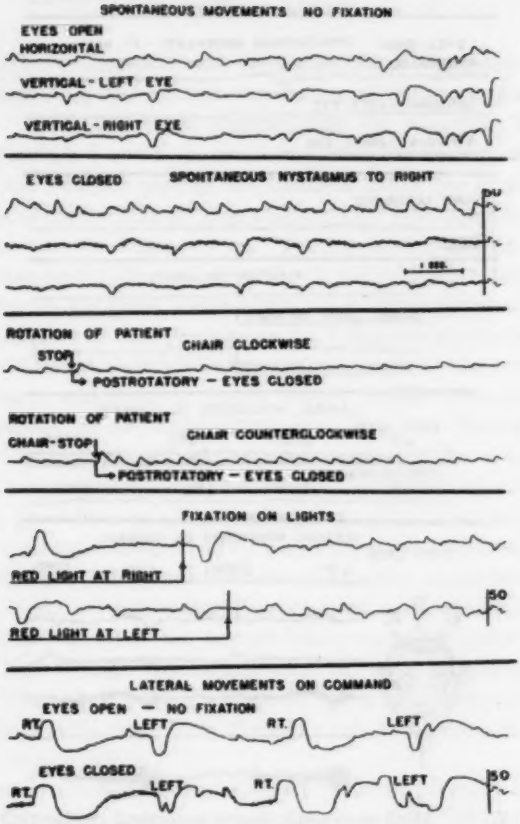


FIG. 4. N. G. 5 days after the left vestibular nerve was cut in a 56-year old woman suffering from Meniere's disease.

Spontaneous movements with eyes open: irregular, scattered nystagmus in either lateral direction, at times of slightly rotary form. Rather frequent normal blinks.

Spontaneous movements with eyes closed: definite spontaneous nystagmus to the right, with some few rotary movements, and occasional small upward twitches of both eyes.

Vestibular stimulation: reduction of nystagmus after clockwise rotation and slight accentuation after counterclockwise rotation.

Fixation on lights in periphery: reduction of nystagmus on looking to the right; accentuation of amplitude but diminution of rate and regularity on looking to the left.

Movements on command: sporadic spontaneous nystagmus, more pronounced on looking to the left.

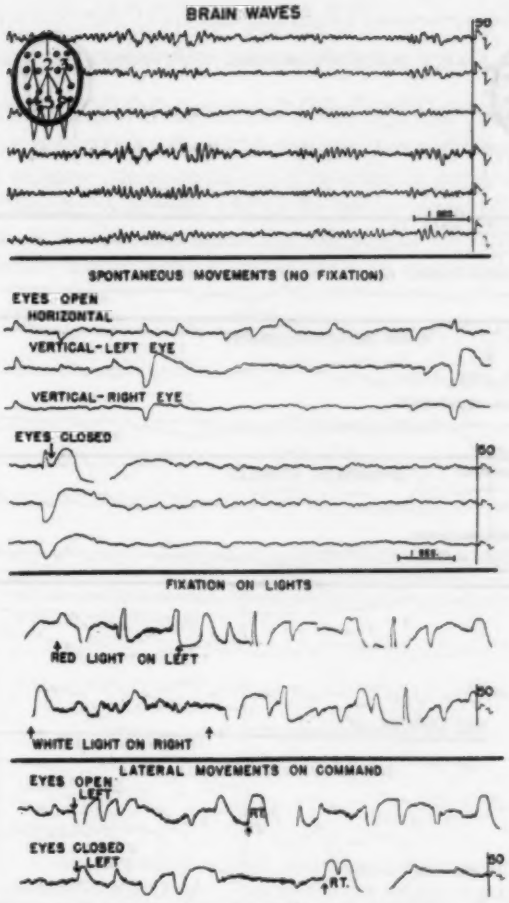


FIG. 5. M. L. Recurrent cerebellar tumor in the left hemisphere, the right lobe having previously been removed almost completely.

Brain waves across the posterior half of the head; some irregular and slightly slow waves in the left temporal region.

Spontaneous movements with eyes open: nystagmus in either lateral direction, with occasional rotary forms.

Spontaneous movements with eyes closed: irregular small wavy fluctuations with disappearance of clear-cut nystagmus. Some reduction of the range of ocular activity in general.

Fixation on lights in the periphery: with the effort of fixation, large and irregular movements, more pronounced on looking to the left.

Movements on command: similar irregularities, more marked on looking to the left, with apparent difficulty in bringing the eyes promptly to a motionless lateral or vertical position.

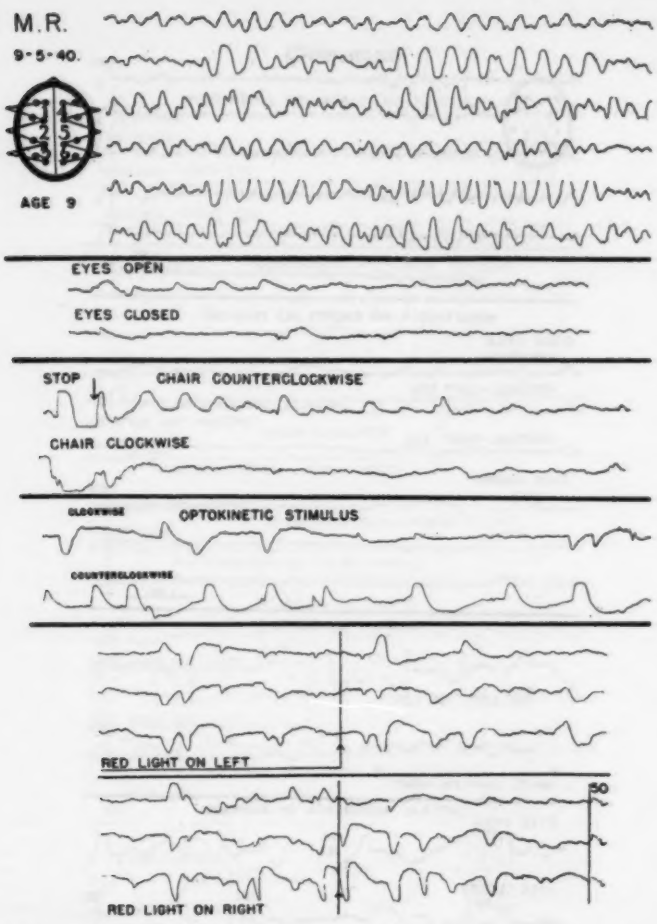


FIG. 6. M. R. Thirteen days after subtotal removal of a cerebellar tumor, requiring extensive excision of the right cerebellar hemisphere in a nine-year old girl.

Brain waves show consistent large and slow waves, maximal in the posterior half of the head.

Spontaneous eye movements with eyes open show intermittent nystagmus, predominantly with quick phase to the right. With eyes closed, all activity including the nystagmus is reduced.

Postrotatory nystagmus to the right is accentuated after counterclockwise rotation and is practically abolished after clockwise rotation.

Optokinetic nystagmus is irregular on looking at the screen rotating to the right, but is much better formed when the screen rotates to the left.

When a red light is presented on one side, there is a definite delay in response, about equal to the left and to the right. Fixation of the eyes on that light brings out coarse irregularities in the eye movements, lasting for some little time after the lights are turned off. They show some nystagmus with quick phase in the direction lateral gaze, more pronounced to the right than to the left.

closed; fixation on lights in the midline, to the right and to the left side (lights in the vertical axis should be arranged but were omitted here on account of some minor technical difficulties in constructing the apparatus); looking to the right and to the left on command but without fixation, first with eyes open and then with eyes closed; and finally in similar fashion looking up and down on command with eyes

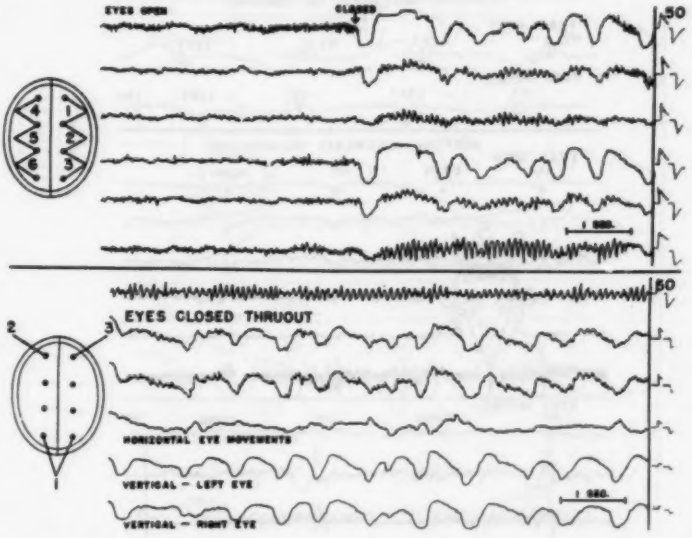


FIG. 7. W. A very intelligent woman, subject to non-progressive dystonic and athetoid movements since birth. This record was one of the early ones and is not complete according to the present system. The upper figure shows the brain waves, in which slow oscillating movements of the eyes are absent when the eyes are open but appear promptly on closing the eyes. They vary somewhat in rate and form but never disappear completely so long as the eyes remain closed. The lower figure shows that these eye movements are almost purely vertical.

open and then with eyes closed. It is quite obvious that there is nothing new in any of these simple tests.

RESULTS

Observations of combined eye movements and brain waves were made in a number of cases. In the graphic records, certain patterns

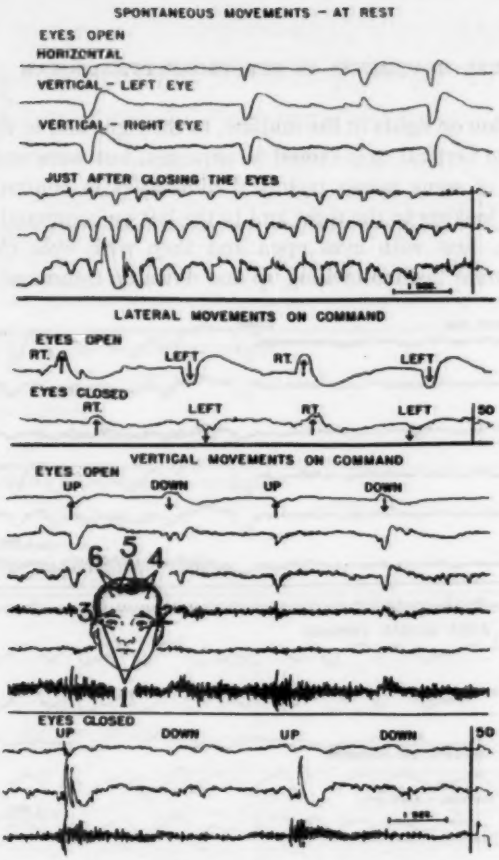


FIG. 8. S. H. Postencephalitic Parkinsonian Syndrome.

Spontaneous movements with eyes open: sporadic nystagmoid movements and rather frequent blinks.

Spontaneous movements with eyes closed: at times a pronounced, somewhat rhythmical, oscillating, vertical tremor appears,—as shown in this figure,—but this does not continue for long; it reappears intermittently; at times it is absent even on closing the eyes.

Lateral movements on command with eyes open: prompt performance in the correct direction but rather small amplitude.

Lateral movements on command with eyes closed: marked reduction of movement, to the point of being barely recognizable.

Vertical movements on command with eyes open: small but prompt movements, the upward being usually worse than the downward.

Vertical movements on command with eyes closed: the uppermost of the bottom three lines represents vertical movements of the left eye (usually absent), the middle line shows those of the right eye (absent, except for consistent abrupt deflections, apparently due to muscular twitches), and the lowest line gives contractions of the frontalis muscles (present during the effort of looking upward).

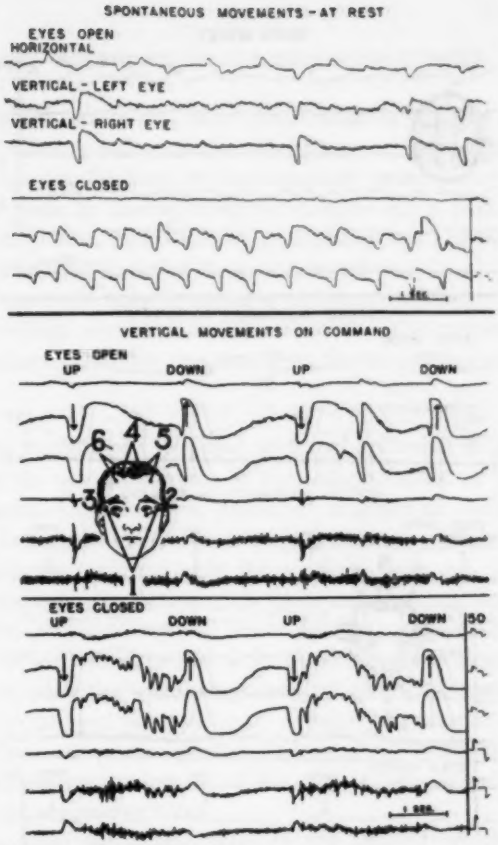


FIG. 9. F.H. Depression in a 64-year old man with some mental symptoms suggesting cerebral arteriosclerosis.

Spontaneous movements with eyes open: frequent but irregular nystagmoid movements in either lateral direction, occasionally rotary. Rather frequent normal blinks.

Spontaneous movements with eyes closed: prompt appearance of a rather regular vertical tremor, which never stops completely so long as the eyes are closed. On opening the eyes this tremor promptly disappears.

Vertical movements with eyes open: fairly well done, although interrupted by somewhat frequent blinks and by some scattered nystagmus.

Vertical movements with eyes closed: consistent difficulty in maintaining the upward position of the eyes after looking up under the closed eyelids. The irregularities after the initial upward movement appear to be a mixture of voluntary effort to keep the eyes in the upward position and of the vertical tremor which is always present in this patient when he is at rest with eyes closed.

(It is a temptation to think in terms of a predominance of extrapyramidal influence in this case,—perhaps a "release" of striatal function,—in view of some evidence for a diffuse cerebral arteriosclerosis which presents some mental and no definite physical symptoms.)

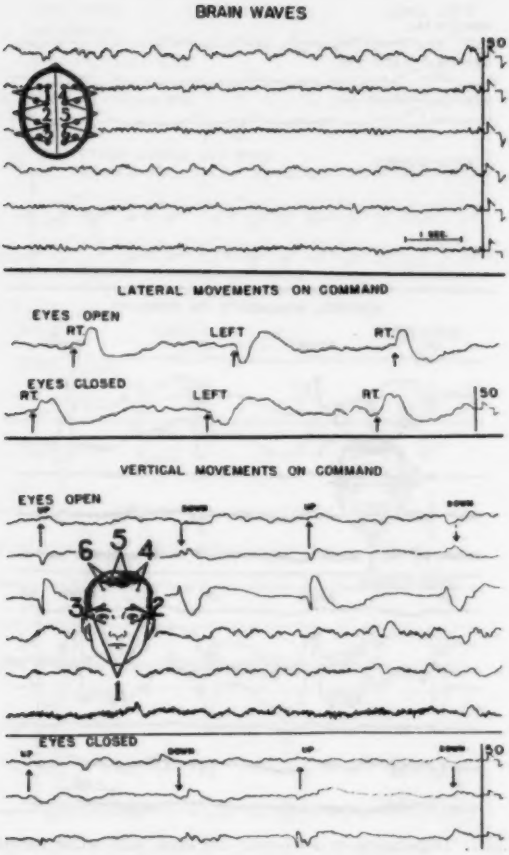


FIG. 10. N. P. G. Bifrontal glioma.

Brain waves: numerous slow waves of increased voltage in both frontal regions, more marked on the left.

Lateral movements on command: with the eyes open, movements are fairly prompt, though of somewhat reduced amplitude. With eyes closed, the movements are slower and accompanied by a feeling that it takes much effort to carry them out.

Vertical movements on command with eyes open: very poor movements, with the left eye consistently showing barely any deviation and the right eye having large but poorly formed deflections. The simultaneous brain waves from the frontal region are clearly not synchronous with the majority of these eye movements.

Vertical movements with eyes closed: the bottom three lines give eye movements only, without brain waves. There is practically no recognizable deviation of either eye in the proper direction. Marked subjective sense of difficulty in carrying out this task.

emerged which seemed to have some relation to the underlying pathology. Others had uncertain significance. These latter did not contradict the implications of the clear-cut pictures but tended to confuse the issue by having abortive changes which were not sharp enough to evaluate, less often by containing mixtures of elements which destroyed the clarity of the primary patterns.

Some of the more definite patterns are presented here. The more pertinent findings are shown in Figs. 3 to 10. The captions identify the main points. Further description in the text seems unnecessary.

DISCUSSION OF RESULTS

The main purpose of this paper is to call attention to possibilities of utilizing the eye movements in the interpretation of the electroencephalogram. The aim is primarily diagnostic. However, the data used in these formulations come from a limited but rather varied series of patients reviewed with the converse logic, *i.e.*, the findings are evaluated *after* the pathological basis has been determined, often by operation. Trial over a long period of time is required to develop a procedure which will be useful and reliable in the desired direction, *i.e.*, starting with the unknown condition which the patient brings to the physician and proceeding to a reasonably certain diagnostic interpretation. Even though the plan presented here has not been put through any protracted test of this sort, it seems worth reporting, if only for its suggestive value.

The procedure for examination of the patient which has been finally chosen for registration of the eye movements is exceedingly simple. It is perhaps much too simple. Further work may demonstrate the need of expanding and also of refining the tests. Already we have developed equipment to supplement certain parts of the examination, in which there are obvious gaps in the simple scheme which has been outlined above. Vestibular stimulation is very important. Caloric irrigation of the ears is the easiest and perhaps the most reliable method and was adopted by us in the past largely for these reasons. Rotation of the patient is now being introduced with simultaneous recording of the eye movements and of the brain waves during and after the rotation. Furthermore a screen with vertical black-and-white stripes can also be rotated around the patient, calling

out ocular movements of attraction, and producing optokinetic nystagmus, which may be graphically recorded in the same way. Lateral tilting of the head, with similar graphic registration, is now being tried out but its value in this setting has not yet been established. Tests of convergence, fusion, etc. hardly seem to be within the scope of electroencephalography, since such functions can be tested so much better by the highly developed technics of ophthalmology.

Already a number of points of interest have arisen in our experience with this method and comments on them will be offered here, taken up in the order of our procedure of examination.

1. *Review the electroencephalogram:* This may give immediate clues but it is unlikely to provide any final information on ocular motility. In addition to the frontal leads where eye movements are best represented, one should inspect the posterior regions for any indication of focal cortical change and for signs of irritation referred to the occiput from some site further peripheral in the visual system. In adults, a unilateral change in one temporal or temporo-occipital region may be of more interest than a midline occipital alteration in cerebellar lesions. It may also lateralize a lesion below the tentorium when the eye movements fail to do so. This stands in contrast to the usual predominance of marked occipital abnormality in children with cerebellar tumors. Mesencephalic and diencephalic lesions seem to have a wider radiation of abnormality, frequently being most prominent in the central regions, but often producing fast waves which come through most clearly in the anterior half of the head on both sides. Blocking of the ventricles alters the picture and seems to cloud the identity of eye movements. Among the patients thus far examined, only one with an old hydrocephalus has gone through a complete examination of ocular motility, thus limiting our experience to only a few incomplete observations in this type of case.

2. *Place electrodes around the eyes and record spontaneous movements,* without fixation, with the eyes open and then with the eyes closed. This gives some freedom to the individual whose distractibility, restlessness, changing attention, or curiosity may lead him to look around the room with eyes open, presenting in some cases a sharp contrast to a relatively quiet record with eyes closed. However, in such cases if nystagmus appears in the graph when the eyes are open, or if there

is any other reason to suspect involvement of the hind-brain or cerebellar system, it may be desirable to reduce the random activity and ask the patient to look ahead without fixating on any particular point. If the nystagmus persists and there is still much more irregular activity with the eyes open than with them closed, one may suspect some suprasegmental vestibular disorder, due perhaps to a lesion of the cerebellum or its connections. Lesions in the cerebellar system often favor an accentuation of motor symptoms during action, but not at rest. However, an increase in ocular activity, together with nystagmus when the eyes are opened, is by no means pathognomonic of a cerebellar lesion. On the other hand, nystagmus which is unidirectional, relatively well sustained with eyes closed (although at times best brought out on closing the eyes after they have been open and moved around in tests), and then reduced or abolished on opening the eyes again, and in which the quick component is toward the healthy side, has occurred uniformly after section of the vestibular nerve in all six cases of Meniere's disease in this series.

A relatively common finding is a tremor of the eyeballs, which appears with the eyes closed, and diminishes or disappears on opening the eyes. It is predominantly if not purely vertical, and is accompanied by more or less blepharospasm (as indicated by the presence of muscular action potentials). It varies somewhat in rate but is usually rather slow (1–4 per second); it may be almost continuous or may occur in runs which subside and reappear. Such tremors do not carry any exact localizing or etiological implication but it is of course possible that there may be a common underlying physiological basis. Fig. 11 shows a few examples of these tremors in cases with widely different diagnoses. Somewhat similar, though often faster and more irregular, vertical tremors with the eyes closed occurred at one time or another in all four of the postencephalitic patients in our series. In one of these patients it was, furthermore, demonstrated that the rate of the ocular tremor was definitely *not* synchronous with the pronounced tremor of rest which the patient presented in his left arm.

Since hyperventilation has been reported as inducing oculogyric crises in patients subject to them from time to time (12), its effect on other forms of extraocular action was tried. This aspect of our work has not been adequately controlled with enough normal subjects or

patients with different diseases. Accordingly no final evaluation can be made at the present time. And yet, two points seem to be quite certain: (a) the appearance of a vertical tremor of the eyeballs on hyperventilation with the eyes closed is not pathognomonic of midbrain disease, since it has occurred immediately after stopping the deep breathing in some normal persons and is, in fact, rather commonly found during the first few deep breaths that many persons take when hyperventilation is being started with the eyes closed; (b) in all cases

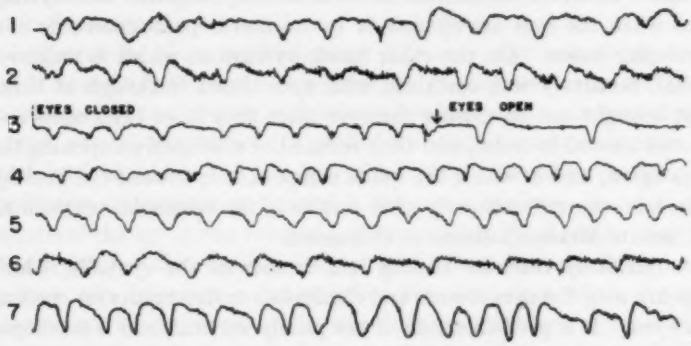


FIG. 11. *Vertical tremors*, appearing with eyes closed, as they appear in the usual frontal leads of the electroencephalograms of patients with widely different diagnoses: 1. Psychoneurosis. 2. Bifrontal glioma. 3. Cerebral concussion with subsequent mental deterioration. 4. Venous aneurysm of the right motor cortex (leg area). 5. Deep vascular lesion, causing dizziness, left hemiparesis, and impairment of hearing in the left ear. 6. Cerebral syphilis with optic atrophy. 7. Chorea in a 54-year old man.

in which the tremor was intensified for a rather prolonged time after the cessation of the deep breathing or in which a protracted accentuation of the tremor followed only a brief period of hyperventilation, either there was known to be some midbrain involvement or else it was quite possible that some disturbance existed in the basal ganglia. Fig. 12 gives two samples of the accentuation or the production of vertical tremor under the closed eyelids as the result of hyperventilation.

3. ***Fixation on lights*** to the right and left side may increase the

general activity of the eye movements and intensify a nystagmus. When this occurs on looking to the side of a suspected lesion, it adds to the suspicion of supravestibular involvement, perhaps of cerebellar origin. If fixation to the contralateral side decreases superfluous

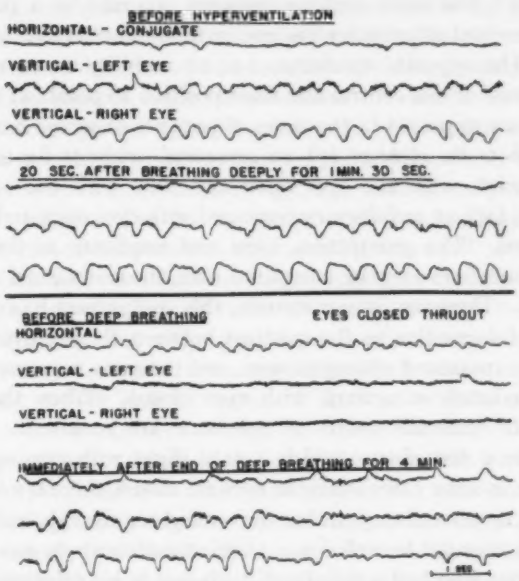

BEFORE HYPERVENTILATION
HORIZONTAL - CONJUGATE
VERTICAL - LEFT EYE
VERTICAL - RIGHT EYE
20 SEC. AFTER BREATHING DEEPLY FOR 1 MIN. 30 SEC.
BEFORE DEEP BREATHING
EYES CLOSED THRUOUT
HORIZONTAL
VERTICAL - LEFT EYE
VERTICAL - RIGHT EYE
IMMEDIATELY AFTER END OF DEEP BREATHING FOR 4 MIN.
1 SEC

FIG. 12. *Effects of hyperventilation.* The *upper pair* of graphs shows a semi-rhythmical vertical tremor of the eyes before hyperventilation in a patient with deep-seated vascular disease (site not exactly determined), and prolonged accentuation of this tremor by hyperventilation.

The *lower pair* shows a predominantly horizontal, irregular, scattered, spontaneous nystagmoid series of movements in a postencephalitic patient before hyperventilation. Immediately after breathing deeply, the horizontal movements diminish and a definite, though short-lasting, vertical tremor appears under the closed eyelids.

movements but tends to bring out a nystagmus, it is compatible with a segmental vestibular abnormality. There may be marked slowness in the patient's response to the appearance of the lights. Although there may be several possible causes of this, the factor of attention must certainly not be overlooked. Inattention seemed responsible

for most of the delays, so far as it could be checked. Rolling movements have also been observed, apparently being an involuntary oscillation around the target as the eyes seek fixation on it. Several examples of this have been noted but none have been adequately explained. The most striking instance occurred in a patient with diffuse cerebral arteriosclerosis, and symptoms referable to the brain stem.[1] The opposite condition, *i.e.*, an inability to move the eyes from a more or less central and fixed position to points at the periphery, has not appeared in the series of patients observed here.

4. *Look to the right or left on command*, without fixation on any special point, with the eyes open and then with the eyes closed. Similarly, *look up and down on command* with eyes open and then with eyes closed. The promptness, form and amplitude of the responses in this procedure may be compared with those obtained on fixation on lights. However, in our records, this comparison has not yielded as much information as the contrast between these movements performed on command with eyes open, and the same movements carried out immediately afterward with eyes closed. When the eyes are closed, the external points of reference are removed. This may accentuate a disturbance which is only slight with eyes open. Furthermore, in some cases when the eyes are closed, there is a feeling that it is hard to move the eyes, that movement requires special effort and even then may not be well done. Unfortunately there was no patient in our series who had a definite disturbance in his orientation toward his body schema. Tests of ocular motility would be particularly interesting in such a patient. In our findings, the *lateral* movements to right and left have seldom brought out striking differences between results with eyes open and those with eyes closed. Some slowing and subjective difficulties in horizontal movements on command, exaggerated by closing the eyes, were met in a patient with a bifrontal tumor (Fig. 10). This is in harmony with clinical experience with some bifrontal lesions (13). However, slowness of response to com-

[1] This patient was examined in the Neurosurgical Clinic but was not operated on. Death occurred four days after discharge from the hospital. Only gross findings at autopsy have been reported at the present time and they showed only a marked generalized arteriosclerosis of the cerebral vessels without evidence of any focal softening on the surface.

mand, together with subjective sense of difficulty in performing the act, again is not a pathognomonic sign of lesions in the frontal area. The patient who voiced the greatest difficulty in moving his eyes under the closed eyelids was a slow-speaking, slightly depressed man suffering from Meniere's disease, without any demonstrable signs or symptoms of a structural abnormality in the frontal region.

The *vertical* movements on command are more interesting than the lateral. They provide a special situation. The mere act of closing the eyes is accompanied by rolling upward of the eyeballs. To ask the patient to look up when the eyes are already turned up under the closed eyelids, sets a more difficult task than looking to the side under the closed eyelids. The eye movements of some individuals were believed on clinical examination to be quite in order and yet there was only a poorly formed deflection in the graphic records when these persons were asked to look up with the eyelids already closed. It is perhaps surprising that really good upward movements are obtained as often as they are under these conditions, and, when they are distinctly good, we are inclined to regard them as evidence of superior control over ocular motility. The group of patients which consistently gave the worst performance in the upward movements on command with the eyes closed was the postencephalitic. An example has already been shown in Fig. 8. The deflections in this group of patients were small, sometimes negligible, much worse when the eyes were closed than when they were open, and considerably worse with upward than with lateral movements performed in the same way. It is interesting that, on questioning this group about the subjective sense of ease in moving the eyes under the closed lids, all four of the postencephalitic patients said they could move their eyes all right and it seemed to them no harder to do so with the eyes closed than with them open. This subjective feeling of ease of performance stands in contrast to the difficulty expressed by the patient with the bifrontal tumor.

One additional picture may have significance. Coming out most clearly during some relatively slow movement of the eyeball, the smooth curve of a normal deviation may be interrupted by saccadic, oscillating or clonic deflections. These may have vestibular, striatal

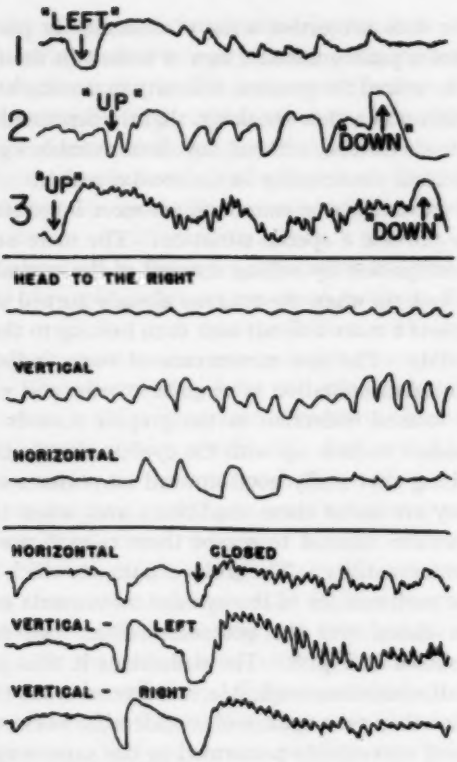


FIG. 13. *Upper group* of three lines:

1. Phasic nystagmus superimposed on an otherwise smooth deviation of the eye to the left where it is held throughout the duration of this sample.

2. Rolling vertical oscillations occurring in a patient with "multiple sclerosis," presenting many brain-stem symptoms, when she looked upward under closed eyelids and held the eyes up until told to look "down" at the place indicated on the graph.

3. Jagged irregularities in holding the eyes in maximal upward position with the eyes closed, in a patient with paresis of upward movements,—presumably representing her effort to overcome the weakness in the elevators of the eyes.

Middle group of three lines: In this group the upper line shows cogwheel resistance of the head to passive rotation to the right. The second line shows synchronous vertical oscillation of the left eye. The third line has some nystagmus, predominantly in the horizontal plane, at the time of maximal acceleration

or cortical origin, with corresponding differences in significance. There may also be still other mechanisms operating in such a picture. In the graphic record a superimposed vestibular nystagmus may be identified by its relatively slow rate, its quick-and-slow phases and by its appearance elsewhere in the record in pure form. On the other hand, irregularly rolling, oscillating interruptions may occur in some cases. These suggest an analogy to the cogwheel resistance of the extremities in patients with extrapyramidal rigidity. In suitable cases these oscillations of the eyes may often be brought out in our records by asking the patients to look in one direction or another, best of all upward with the eyes closed. Even in those who show pronounced oscillations, the initial movement of the eyes to the desired position is usually free from these interruptions, which may then appear rather strongly when active movement stops and the patient is merely trying to hold the eye motionless in the eccentric position. The nature of these oscillations was sought by a further procedure with one of the postencephalitic patients who had them especially clearly. He sat in the screened cage and was asked to look off into the distance and to keep looking steadily in much the same direction, but without fixating on any definite spot. The examiner stood behind him and slowly and evenly rotated the head of the patient back and forth. The observer could feel a very distinct cogwheel resistance to rotation of the head, increasing as the extreme lateral positions were approached. The graphic record (Fig. 13) demonstrated not only the existence of this cogwheel phenomenon of the head, but also a strictly synchronous vertical tremor of the left eye (movements of the right eye were not recorded), and, in addition, the totally different picture

---

of the rotation. This nystagmus also appears in the second line,—hence, a rotary nystagmus,—but its form and rate are clearly different from those of the "cogwheel" tremor in the vertical axis of the left eye. No record was made at this time from the right eye.

Lower group of three lines: Patient with postencephalitic Parkinsonism. Frequent blinks when the eyes are open. On gently closing the eyes, the orbicularis phenomenon appears as a moderately fast and fairly regular tremor with slight superimposition of muscular components, occurring simultaneously in the vertical *and horizontal* leads,—in contrast to the strictly vertical and slower oscillations in the middle lines of the two groups, shown above in this figure.

of nystagmus in the horizontal plane. It is immaterial to the present argument whether this nystagmus is based on a slow optokinetic, a slow rotational labyrinthine, or a tonic neck-reflex mechanism. The point is that this patient, who had previously shown similar vertical oscillations of about this rate when asked to look up and keep looking up, now has these oscillations under conditions which imply an origin in the basal ganglia. These rather regular, vertical deflections, resembling sine waves and synchronous with palpable cogwheel resistance to movement of the head, should be sharply distinguished from the smaller and faster oscillations, often irregular and containing many pointed forms, which occur in some persons when they look upward under the closed lids or even when they merely let the eyelids drop slowly closed (Fig. 13). Since this latter picture can be shown to exist quite as much in the horizontal as in the vertical axis, it is believed to be produced by the activity of the orbicular muscles of the eyes. Described by Bergara and independently by Wartenberg (14, 15), a "tetanic" contraction of the orbicularis oculi can be palpated in all healthy persons but is absent during and for some time after a facial paralysis. It seems that our interest in this orbicularis phenomenon relates to its overfunction, whereas Bergara and Wartenberg were originally attracted by its underfunction. However that may be, its full mechanism has not yet been explained to our satisfaction. In our records it has been found occasionally in healthy subjects, more often in patients who have more or less trouble in upward movements of the eyes, and uniformly and most markedly in our postencephalitic group. In spite of an immediate origin in the orbicularis muscles, it may still have a close relationship to actual vertical movements of the eyeball, in view of the intimate connection between the structure and function of these muscles and those of the extra-ocular muscles controlling the vertical action of the eyes. In Fig. 13, samples are given of phasic nystagmus superimposed on a smooth deviation of the eye, of rolling oscillations, and of irregular jerky deflections accompanying the voluntary act of looking upward when effort was required to overcome paresis of vertical upward movements.[2] In Fig. 13, there is also an excerpt from the demonstration that rhythmical oscil-

[2] The privilege of getting records from this patient and of comparing our findings with his clinical examination was extended by Dr. Frank B. Walsh.

lations of the eye may be synchronous with palpable cogwheel resistance to rotation of the head.

DISCUSSION OF INTERPRETATION

There are a few pictures in the graphs of eye movements which have fairly specific physiological implications,—such as spontaneous deflections indicating *focal irritation or spasm*. Reliability is added if these occur in "attacks,"—have a definite onset, course and subsidence with return to the previous pattern,—and especially if they occur in only one eye and are accompanied by subjective awareness of the attack by the patient. The exactness with which they can be

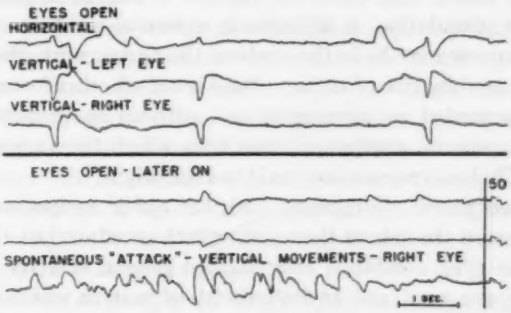


FIG. 14. Spontaneous "attack" of nystagmoid vertical movements of the right eye only, in a patient with an anomalous vessels from the Circle of Willis, entering the midbrain in the region of the right oculomotor nucleus.

assigned to particular anatomical spots depends on what is known in general about the representation in the brain stem of the particular functions involved. One example is given in Fig. 14 which shows an irregular nystagmoid attack of spontaneous vertical movements of the right eye in a patient with an anomalous vessel from the circle of Willis which implicated the right oculomotor region. However, so far as we know, there is no single phenomenon which gives etiological diagnostic significance to the eye movements; nothing comparable to the spike-and-wave pattern in the electroencephalogram, in the diagnosis petit mal epilepsy (16).

A marked reduction or total absence of deflection during deviation

of the eyes in some one direction (especially lateralward) may indicate a definite *focal defect*. This is convincing only when it is striking and consistent, and perhaps also if it exists only unilaterally so that the other side can serve as control. However, we have paid rather little attention to such findings, since they can be determined so much better by the ordinary clinical methods of examining the eyes.

Phasic nystagmus is easy to recognize in these records. Combining our results with general clinical experience, one picture stands out fairly clearly. When the nystagmus is rhythmical, spontaneous and definite with eyes closed, when it is reduced or abolished on opening the eyes, when the quick phase is toward the side opposite to the suspected lesion, and when the rhythm is altered appropriately by vestibular stimulation, it indicates a *segmental vestibular involvement*, which of course may be in the nucleus, the nerve trunk, the labyrinth, or in any combination of these. Most if not all other forms of nystagmus are regarded as suprasegmental, without assignment as yet to any of the several anatomical sites from which the various supranuclear vestibular syndromes are said to take origin.

Scattered phasic nystagmus, with the quick component predominantly toward the side of the lesion, which is reduced or abolished by closing the eyes, combined with marked general activity of the eyes when they are open, and an irregularity of pattern which is increased on carrying out tasks such as coming to fixation on spots in the periphery of the visual fields, should raise the question of a lesion in the *cerebellum or its immediate connections*. However, our experience with this type of case has been limited and we do not offer this as a description of adequately tested reliability.

Dissociation of ocular motility in the horizontal plane has not offered much of interest so far. In the vertical axis there have been numerous instances of slight but definite movements of one eye and not of the other *when the eyes are closed*. The significance of dissociation under these conditions is not certain but we are inclined to view it as an intermediate stage between the strict conjugate action of alertness with eyes open and the drifting dissociations which may occur normally in sleep. On the other hand, a few clean-cut instances of vertical dissociation have occurred, definite when the eyes are open and striking when the eyes are closed, in which the

clinical histories were at least compatible with the assumption of some physiological abnormality in the midbrain in the *neighborhood of the oculomotor nuclei.*

In this discussion so far, *single criteria* have been considered separately in the interpretation of our records of eye movements. No other single features in the graphs seem to have special significance in localization, although many may serve as general guide posts,—such as the pronounced accentuation of a vertical tremor by hyperventilation, etc.

Further interpretation calls for consideration of *patterns or groups of interacting functions* when the normal equilibrium has been disturbed by some lesion.

A number of items appear in the graphic records of ocular motility, especially when they are studied in conjunction with simultaneous brain waves. From these, a selection may be made and arranged schematically in tabular form, as a convenient way of combining groups of items in a condensed form of presentation. It is expected, of course, that with increasing experience the use of such a table will give way to a process in which many short-cuts may be made in weighing and choosing the factors of dominant importance in a more flexible sorting out of the various components.

The single item of greatest interest in our method appears to be in the *vertical* action of the eyes. An abbreviated series of three simple observations can be made with this function alone:—looking upward on command with the eyes open, closing the eyes with the associated rolling upward of the eyeballs, and the further task of looking upward with the eyes closed when the eyeballs are already turned up under the closed eyelids. Fig. 15 gives graphic comparisons of the results obtained with these three types of upward movements in different patients.

A more complete scheme would include some items which go beyond those appearing in the records of eye movements alone. Contraction of the frontalis muscles comes out very clearly when our standard connections, shown in Fig. 1, are made. If there is definite frontalis contraction with each upward movement of the eyes, there can be no doubt about the (cortical) initiation of the act. At least some effort is expended. Failure of the eyeballs to move upward must then be

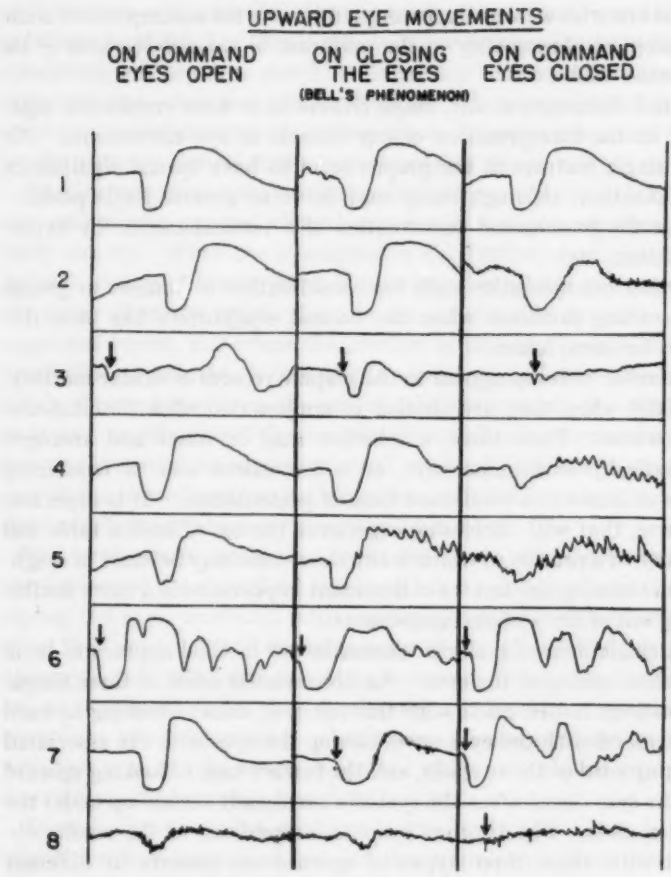


FIG. 15. *Upward eye movements.*

1. An intelligent 16-year old girl, congenitally deaf. Very good eye movements throughout. Instructions were given to her in writing and then she would close or otherwise move her eyes accordingly, when tapped on her shoulder.

2. Meniere's disease. Very good movements, except for slight flattening of the curve when looking upward under closed eyelids, together with some few muscular action-potentials. The patient volunteered that it was very difficult for him to move his eyes when they were closed and he thought he did it very poorly.

3. Bifrontal tumor. Only Bell's phenomenon is adequate and even that is

assigned to a disturbance below the highest cortical level. The brain waves themselves may contribute evidence of some lesion at or near the surface of the cerebral cortex. And finally, the subjective feeling of ease in performance carries in some cases a rather definite implication. If eye movements are very poorly done, especially under the closed eyelids, and if there is a marked sense of difficulty in carrying them out, some higher (cortical) mechanism is suspected, especially if the presence of frontalis contractions at the time of the effort shows that the task was understood and attempted. In contrast, if the eye movements are quite poorly done with the eyes closed and yet the patient feels that they were easily and well performed,—as occurred in all the postencephalitic patients in this series,—another, lower, mechanism is involved, perhaps implicating proprioceptive function in the ocular muscles. All these items appear in Table I, which is offered with the warning that it has recognized limitations.

Consideration of the role of the *cerebral cortex* in eye movements brings out at once the absence of any instance of involuntary conjugate deviation in our records. This important symptom needs no graphic registration, however. In all the patients with frontal lesions, on whom

---

somewhat smaller in amplitude than usual. The arrows indicate when the commands were given. The exceedingly poor responses were accompanied by a marked sense of difficulty in their performance.

4. Medical student who wears glasses for myopia but has no disturbance of extraocular muscles. Consistently poor upward movements with the eyes closed. The orbicularis phenomenon comes out definitely at those times. (See text.)

5. Postencephalitic patient. Rather poor upward movement under the closed eyelids, although she thought her eyes moved as well as when her eyes were open. The orbicularis phenomenon is marked and prolonged in looking upward with the eyes closed and is present also when she merely closes her eyes.

6. "Multiple sclerosis," with brain-stem symptoms. Slow and rather regular oscillating interruptions when holding the eyes in upward position with eyes open. Small oscillations on closing the eyes. Big, coarse, prolonged and irregular oscillations when trying to keep the eyes upward under the closed eyelids.

7. Multiple sclerosis, with paresis of upward movements (Dr. Walsh). Good movements with eyes open, fair on closing the eyes, but irregular deflections, implying effort, in trying to hold the eyes up under the closed eyelids.

8. Blind since birth. Only small movements on command with eyes open and on closing the eyes. Mere muscular contractions, corresponding to visible quivering of the eyelids, when trying to look up with the eyes closed.

TABLE I

	CLOSING THE EYES (BELL'S)	LOOK UP EYES OPEN	LOOK UP EYES CLOSED	SPONTANEOUS ACCESSORY MOVEMENTS	RESPONSE TO VESTIBULAR STIMULATION	FRONTALIS CONTRACTION (ON LOOKING UP)	SLOW BRAIN WAVES	SUBJECTIVE SENSE OF EASE
Normal person	Good	Good	Good	None	Norm.	Good	None	Good
Normal—but with individual variation	Good	Good	May be fair, or poor	None	Norm.	Good or bilat. poor	None	Good or poor
Normal—but inattentive or uncooperative	Good	Good, fair or poor	Variable	None or random	Norm.	Variable, often poor	None	?
Facial paralysis	Good	Good	Good	None	Norm.	Unilat. absence	None	Good
Segmental lesion at level of oculomotor nucleus	Poor or fair	Poor or fair	Poor	Only muscular spikes around eyes	Reduced or absent	Good	Probably none	Probably poor
Lesion at or near the oculomotor nucleus, with irritative pathology	Good, fair or poor	Good, fair or poor	Fair or poor	Sporadic vertical or dissociated vertical movements; perhaps defective vertical excursions	Norm. or various changes	Good	Probably none	Probably poor
Supranuclear-striatal lesion	Rather good	Fair or poor	*Poor*	Oscillations, espec. on looking upward; spontaneous vertical tremor with eyes closed; exagger. orbicularis phenom.	Various slight changes	Good, or excessive or continuous	Usually some irregularities	Usually *good*
Supranuclear-cortical or cortical projections	Good	Good or fair	Good, fair or poor	Conjugate horiz. spasmodic fixation. Occas. irregular and varying nystagmus	Usually norm.	Usually good	May show focal change over the lesion	Good or poor
(Bi)frontal lesion	Fair	Fair or poor	*Poor*	Usually only rambling movements; little or no nystagmus	Slight changes, if any	Good or fair	Usually definitely present	*Poor*

No attempt is made here to use various forms of nystagmus or of other vestibular responses in further subdivision of the sites of lesion (17, 18).

records of ocular motility were made, there were definite, spontaneous, irregular if not random movements, usually with quiet intervals of varying duration, and typically without phasic nystagmus. Slowness and subjective difficulty in moving the eyes on command have been noted, especially with frontal lesions, but also with lesions elsewhere in the cortex (*e.g.*, in one patient with a glioma in the right parietal region involving the motor cortex, and in another with a right-sided vascular lesion at the occiput).

Beyond findings of this relatively simple sort, the cerebral cortex provides increasing possibilities of variation and complexity with a widening of the scope of examination. In addition to the very gross changes which occur, for example, with alterations of consciousness, as has been demonstrated in shock therapy for schizophrenia, there seems to be a range of less pronounced change, more difficult to evaluate, which relates to the finer adjustments of the eyes in their function as our most important effector organ of orientation. From viewing simple spacial relationships of one object to another, one would like to pass to performances more heavily loaded with symbolic significance, such as reading, perceiving the bases for our appreciation of pictorial art, etc. This paper ends by arriving at, but not entering, the field of the psychophysiological interpretation of ocular movements.

SUMMARY

The electroencephalogram records directly from the surface of the cerebral cortex only. Eye movements add observations on a subcortical function. Limitations of interpreting ocular motility in electroencephalograms, without electrodes put around the eyes, are pointed out.

A very simple procedure has been used for collecting data on the eye movements. It is described, and examples showing its clinical utility are given.

Not enough examinations have been made by means of the new procedure to permit an accurate evaluation of the diagnostic implications. In interpreting the records, attention was first directed to the selection of a few single features of significance, and then groups of findings were provisionally arranged as patterns of various interrelated

No attempt is made here to use various forms of nystagmus or of other vestibular responses in further subdivision of the sites of lesion (17, 18).

functions. Tentative conclusions have been reached regarding the pathological significance of certain types of records, especially those in which the vertical eye movements with the eyes open were contrasted with the vertical movements with the eyes closed.

I wish to thank Dr. Walter E. Dandy for permission to make use of his patients in carrying out these studies. Both Dr. Dandy and Dr. Kenneth L. Pickrell gave valuable assistance in discussing with me the histories of patients, and the operative findings. I wish also to thank Dr. Hans Loewenbach for his constructive criticism of the results.

REFERENCES

1. Myers, I. L.: Electronystagmography. A graphic study of the action currents in nystagmus. *Arch. Neurol.* **21:** 1929: 901–918.
2. Jacobsen, E.: Electrical measurements of neuromuscular states during mental activities. III. Visual imagination and recollection. *Am. J. Physiol.* **95:** 1930: 694–702.
3. Mowrer, O. H., Ruch, T. C. and Miller, N. E.: The corneo-retinal potential differences as a basis of the galvanometric method of recording eye-movements. *Am. J. Physiol.* **114:** 1936: 423–428.
4. Fenn, W. O. and Hursh, J. B.: Movements of the eyes when the lids are closed. *Am. J. Physiol.* **118:** 1937: 8–14.
5. Halstead, W. C.: A method for the quantitative recording of eye movements. *J. Psychol.* **6:** 1938: 177–180.
6. Baudouin, H., Fischgold, R., Caussé, R. and Lerique, J.: Un vieille notion trop oubliée: la différence de potentiel rétino-cornéenne, son intérêt théorique et pratique. *Bull. Acad. de méd.* **121:** 1939: 688–693.
7. Jung, R.: Eine elektrische Methode zur mehrfachen Registrierung von Augenbewegungen und Nystagmus. *Klin. Wochenschr.* **18:** 1939: 21–24.
8. Hoffman, A. C., Wellman, B. and Carmichael, L.: A quantitative comparison of the electrical and photographic techniques of eye-movement recording. *J. Exper. Psychol.* **24:** 1939: 40–53.
9. Leksell, Lars: Clinical recording of eye-movements. *Acta chir. Scand.* **82:** 1939: 262–270.
10. Lovell, H. W., Czarski, T. J. and Lyman, R. S.: The effect of vestibular stimulation on brain waves. *Chinese J. Physiol.* **14:** 1939: 389–410.
11. Perlman, H. B. and Case, T. J.: Nystagmus: some observations based on an electrical method for recording eye movements. *Laryngoscope* **49:** 1939: 217–228.
12. Georgi, F.: Ungewöhnliche postencephalitische Symptombilder, zugleich ein Beitrag zur experimentellen Erzeugung sog. Schauanfälle. *Ztschr. f. d. ges. Neurol. u. Psychiat.* **106:** 1926: 602–612.

13. HOLMES, GORDON: The cerebral integration of the ocular movements. *Brit. Med. Jour.* 2: 1938: 107–112.
14. BERGARA, CARLOS: Ein neues Symptom der Facialislähmung. Ref. *Zentralbl. Neurol. u. Psychiat.* 55: 1930: 512.
15. WARTENBERG, R.: Ein Symptom der Facialislähmung. *Dtsche Ztschr. f. Nervenh.* 116: 1930: 144–145.
16. GIBBS, F. A., GIBBS, E. L. AND LENNOX, W. G.: Epilepsy: a paroxysmal cerebral dysrhythmia. *Brain* 60: 1937: 377–388.
17. BIELSCHOWSKY, A.: Symptomatologie der Störungen im Augenbewegungsapparat. *Handb. der Neurol.* Bd. IV; Teil IV/2. Berlin, 1936, 186–266.
18. MUSKENS, L. J. J.: *Das supravestibuläre System.* Amsterdam, 1934.

TYPE I PNEUMOCOCCAL PNEUMONIA

Clinico-immunological Studies with Special Reference to the Rationale of Combined Serum and Drug Therapy[1]

JAMES W. HAVILAND, M.D.

From the Biological Division of the Medical Clinic of The Johns Hopkins Hospital

Submitted for publication August 5, 1940

With the efficacy of chemotherapy of pneumococcal infections firmly established by numerous clinical studies during the past year, it has become necessary to revise current conceptions of the optimal method for the treatment of pneumonia so as to include that which is good in two very excellent forms of specific therapy, *i.e.*, type-specific anti-pneumococcic serum, and drugs, such as sulfapyridine and sulfathiazole. By such revision it is to be hoped that there will be derived a method of therapy which not only will include the good features of both forms of therapy but also will be devoid of their untoward reactions.

On solely theoretical grounds it would appear that a combination of these therapeutic agents would be superior to the use of either one alone. In the first place, their action on the pneumococcus is different. Serum probably acts by providing opsonins so that the organisms may be more easily phagocytized. So far as can be determined at present the drugs act by a bacteriostatic effect on the pneumococci, while the ultimate destruction of the bacteria is accomplished by lysis or by phagocytosis. In the second place, if it be permissible to argue by analogy, since combined drug and serum therapy have been shown to act to better advantage in experimental meningococcic infections (1, 2), it seems plausible that the same might hold true in pneumonia. Furthermore, drug reactions constitute a potential hazard which must be considered if therapy is to be continued over a period of several days. Ideally, therapy ought to be planned in such a manner as to

[1] Expense for this study was defrayed by a grant from the Chemical Foundation, Inc., of New York City.

produce its desired effect as soon as possible, and then to be stopped before the untoward reactions, which might result from treatment, have had an opportunity to put in an appearance. With the use of serum alone, case fatality rates have remained at an undesirably high figure except in certain small groups of cases (3). By itself, therefore, this form of treatment has not been entirely satisfactory. Hence, it has seemed desirable to make observations on the concurrent use of type-specific antiserum and drugs in the treatment of pneumonia.

In undertaking this study of combined drug and serum treatment, it was hoped that a more effective scheme of therapy for pneumonia might be determined. Such a scheme would provide a lower mortality rate, a more rapid recovery from the disease, a lower incidence of complications, as well as of drug reactions, and, in addition, it would provide criteria for an optimum dosage of both agents which would keep the expense of specific therapy within reasonable bounds.

METHODS

A. *Drug Administration.* The drug which was chosen for use in any particular case was administered by mouth whenever possible. The customary dosage was 4 grams initially, followed by 1 gram every 4 hours. In the event that the patient was critically ill or unable to take the drug orally, the sodium salt of either sulfapyridine or sulfathiazole was given intravenously, the initial dose being approximately 0.06 gram per kilogram of body weight (4). Subsequently the administration was carried on by the oral route as soon as this was feasible. Blood level determinations were made daily for both free and combined drug. As soon as the patient's clinical condition warranted the change, the dose of drug was halved and finally stopped. During the latter part of the year when the results of the antibody studies became available, the drug was stopped 24–48 hours after the patient's temperature dropped to normal.

B. *Serum Administration.* After the history for allergy had been taken, the patient was subjected to the recommended tests for serum sensitivitiy. As soon as the appropriate interval had passed and the tests were adjudged negative, the total dose of 100,000 units of type-specific anti-pneumococcus serum was given intravenously in a single injection. Blood samples were drawn at frequent intervals for some days thereafter to be tested for antibody content by the various methods. In those cases in which the patients received larger quantities of serum the plan of dosage was identical with that previously outlined for this clinic by Wood (5), using the Francis skin test with specific capsular polysaccharide when available.

C. *Antibody Determinations.* (a) Mouse Protection tests were performed as described by Felton (6) and later by Wood (7). The general plan was to use a

standard dilution of serum and to titrate its antibody content against various concentrations of virulent type I pneumococci. The results tabulated in this report are given in terms of units of antibody per c.c. of patient's serum where the unit of protective antibody is defined as that amount of serum which will protect 50 per cent of a group of mice for 36–48 hours against 1,000,000 MLD. Groups of 5 mice were used for each titration point in this work. (b) Microscopic agglutinations were performed on almost all samples of blood. These determinations were made by a modification of the Sabin rapid slide method (8). The technique here employed, however, was that of mixing a loopful of actively growing organisms with a loop of methylene blue and then with 2 loopfuls of the sample of serum. The cover slip was then inverted and sealed on a hollow-ground slide and viewed with a microscope after one-half hour as a hanging drop. (c) The so-called "thread tests" were performed after the method described by Paul (9). In brief, it consisted of an examination of the flocculation which occurred when actively growing pneumococci were incubated with type-specific serum for several hours and then refrigerated for at least 8 to 12 hours. (d) Francis skin tests with the specific capsular polysaccharide were done daily whenever possible and they were interpreted as described previously (5). (e) Precipitin tests with specific polysaccharide were done in some cases as a check. Aliquots of undiluted serum and capsular polysaccharide (diluted to 1–10,000, 1–20,000 and 1–50,000) were tested by mixing, allowing the mixture to stand at room temperature for 2 hours and then refrigerating the mixture overnight (10).

EXPERIMENTAL RESULTS

Several reports have appeared concerning the advantage gained experimentally by using a combination of serum and drug therapy (11, 12). A few experiments were set up which were designed to show what degree of improvement in protection might be expected by combined therapy, as well as what relative effects might be obtained by administering serum before using drug and *vice versa*. A type I antipneumococcus rabbit serum to be used for these observations was very kindly supplied by The Lederle Laboratories, Inc. The potency of this serum was found to be about 7.5 units per c.c.

0.5 c.c. of a 1–5,000 dilution of this serum would afford protection to 50 per cent of mice for 48 hours after the intraperitoneal injection of about 400 virulent Type I pneumococci, while the untreated controls and those treated with 0.5 c.c. of a 1–15,000 dilution of serum died within 15–18 hours. Sulfapyridine fed by stomach tube would protect similarly infected mice for about 96 hours, but at this point the test animals would die off rapidly despite continued administration

of the drug. (The quantity of sulfapyridine (15 mgms.) was given as a 3 per cent suspension in acacia twice a day for 3 days, and once a day thereafter.) It was found that the amount of serum which was

TABLE I

Effect of combined drug and serum treatment on mice experimentally infected with Type I pneumococci

DILUTION OF SERUM*	#1†	#2‡	#3§	#4¶	#5‖
Drug					1 D, 4 S } at 96 hours 5 D at 120 hours
1–5,000					2 D, 3 S } after 48 hours
1–15,000					4 D, 1 S } after 48 hours
1–30,000			1 D 4 S		
1–40,000			1 D 4 S		
1–50,000	9 D 11 S	14 D 1 S	7 D 8 S	5 D	
1–60,000	9 D 6 S	15 D	12 D 3 S		

D = Mice died, S = mice survived.

* 0.5 cc. of various dilutions of sera were injected intraperitoneally.

† Sulfapyridine administered at same time mice were infected. After a lapse of 4 hours, serum was administered intraperitoneally.

‡ Serum administered at same time mice were infected. After a lapse of 4 hours, sulfapyridine was administered orally.

§ Serum and sulfapyridine were both given at same time the mice were infected.

¶ Mice were infected. After a lapse of 4 hours serum and sulfapyridine were given.

‖ In these experiments the drug or the serum were used alone and not in combination.

Note: Survival in all these experiments was determined at 120 hours except as noted in column #5.

required to afford protection to 50 per cent of the mice for 120 hours, if used in combination with the same dosage of drug and infecting organisms, could be reduced to 0.5 c.c. of a 1–50,000 dilution of the

same serum. When a 1–60,000 dilution of serum was employed, however, satisfactory survival rates could not be obtained (Table I).

It was further observed that the enhanced protection which was conferred when the drug was given 3 or 4 hours prior to the serum administration (provided that the first dose of drug was administered at the same time as the infecting organisms) was afforded to approximately the same degree when the serum and sulfapyridine were given at the same time. In the event that serum was administered 4 hours before the drug, on the other hand, no protection could be detected with these quantities of materials. This last observation also held true if both serum and sulfapyridine were administered together about 4 hours after the mice had received their infecting dose. Blood cultures taken just before treatment in this last group were found to be positive. In view of this work it was thought that the most efficacious method of combining the two therapeutic agents would be to start the drug administration immediately, then to follow with serum after several hours had elapsed. The work also suggested that the dose of serum could be reduced to one-third or one-fourth the ordinarily accepted therapeutic amount, provided the infection was not already too severe.

CLINICAL RESULTS

To carry out this work on combined drug and serum therapy, it was planned to use all the available cases of type I pneumonia in this clinic as a sample group. The experience with type I pneumonias reported by other workers was to be used as a control. Table II shows, however, that only 20 of the 39 type I pneumonias admitted this year were treated in accordance with the general scheme to be outlined below (i.e., drug plus 100,000 units of type I anti-pneumococcus serum). These cases comprise Group I. The five cases in Group 2 that received more than 100,000 units of serum in divided doses were adjudged too ill on admission to warrant anything but the most intensive treatment. It seems likely in retrospect that at least two, and probably three of these five cases might have been safely included in Group 1. The single patient who received only serum (Group 3), was a colored female who had had a fairly severe febrile reaction while under treatment with sulfathiazole for generalized

peritonitis some two weeks before her admission with lobar pneumona. It was not considered wise to attempt drug therapy in her case. At first, Group 4 was composed entirely of patients from whom a type-specific pneumococcus was not obtained immediately. When that organism was finally recovered, the patient's general condition did not warrant the use of serum to aid the previously instituted drug therapy. Later, cases were included in order to study the development of antibodies. It was desired to compare the results obtained by means of the method reported by Kneeland and Mulliken (10) with those obtained by the methods earlier reported from this clinic (7). Fairly complete observations on these points were made in seven cases in this particular group.

Before attempting to analyze the whole group as tabulated, it will be worthwhile to outline in greater detail the plan of therapy used in the cases of Group 1. The figures from 15 series of type I pneumonia cases were obtained from the literature. These spanned the period from 1928 through 1939 and were reported in such a fashion as to lend themselves to analysis as far as concerned average dosage. In general, during recent years, the average amount of serum given each patient had increased. Finland (13) some years ago, stressed the need for the early use of adequate amounts of serum if case fatality rates were to be lowered, and the results which were being achieved just prior to the introduction of sulfapyridine seem to bear out the importance of his contention. By averaging all the therapeutic recommendations from these 15 reports, it appeared that about 200,000 units constituted a satisfactory estimated dose for an uncomplicated case. In view of the experimental evidence which was detailed above, it was decided to use only 100,000 units in the present series. The next problem which required a decision was whether that amount of serum ought to be given in several small doses and the whole procedure followed carefully by the Francis skin test as suggested by MacLeod (14) and Wood (15), or whether it ought to be given in one single injection as advised by Loughlin (16) and Blake (17). Inasmuch as it was considered that the administration of only 100,000 units of serum would be insufficient to neutralize the circulating capsular polysaccharide, it seemed likely that the Francis skin test would not be of much value, no matter which plan was used. At the same time

TABLE II

Type I pneumococcus pneumonias—1939–40—J. H. H.

SERIES NO.	AGE	SEX	COLOR	NO. LOBES INVOLVED	DAY OF DISEASE TREATMENT STARTED	BLOOD CULTURE	DRUG USED	DURATION OF DRUG TREATMENT	AMT. SERUM IN 100 M's	RESULT	COMPLICATIONS AND REACTIONS	INTERCURRENT DISEASE	ANTIBODY TITRES OF PATIENTS' SERA			
													Units per cc.	Appearance time	Duration*	Titre before Treatment
1. Cases treated with drug plus serum—100,000 units or less																
								days								
35 R.H.	26	M	C	1	4th	N	S-P	9	1.0	Crisis	Severe accelerated serum reaction		0.1–1.0	Immediately	5	0
40 S.D.	43	M	W	1	3d	N	S-P	4	1.0	Crisis	Serum sickness on 7th day, microscopic hematuria		0.1–1.0	"	6	0
52 H.S.	58	M	W	1	3d	N	S-P	4	1.0	Crisis	0	Bladder tumor	>0.7	"	10	0
53 T.K.	22	M	W	1	2d	N	S-P	5	1.0	Crisis	0		>0.7	"	5	0
79 B.A.	40	F	W	1	8th	N	S-T	2	1.0	Crisis	Serum sickness on 7th day		>0.7	"	2	0
84 W.P.	24	M	C	2	2d	N	S-T	2	0.6	Crisis	0		>0.7	"	2	0.1
90 R.B.	26	M	C	1	2d	N	S-P	10	1.0	Crisis	0		>0.7	"	5	0
94 E.C.	36	M	W	1	5th	N	S-P	4	1.0	Lysis	0		>0.7	"	5	0.02
96 R.H.	26	M	C	1	3d	10	S-T	9	1.0	Crisis	Microscopic hematuria. Serum sickness 9th day		>0.7	"	8	0
107 B.D.	24	F	W	1	3d	N	S-P	3	0.45	Crisis	Accelerated and delayed serum disease, drug fever					
127 W.G.	36	M	C	1	3d	N	S-P	5	1.0	Crisis	Accelerated serum reaction		>1.0	"	2	0
129 A.G.	50	M	C	1	1st	N	S-P	3	1.0	Crisis	0		>1.0	"	4	0
130 M.G.	24	F	C	3	7th	N	S-P	5	1.0	Crisis	Hematuria, serum sickness		>0.7	"	9	0.002
135 L.C.	17	M	C	1	1st	N	S-P	6	1.0	Crisis	0		>0.7	"	4	0
156 J.C.	17	M	W	1	3d	N	S-P	5	1.0	Crisis	Transient oliguria		>0.7	"	4	0.002
181 P.A.	29	F	C	2	3d	11	S-T	8	1.0	Lysis	Empyema	Empyema on admission 5 days post-partum	1.0	"	8†	0
189 A.G.	21	M	C	1	3d	N	S-P	2	0.5	Crisis	Severe accelerated serum reaction, hematuria	Azotemia	>1.0	"	8	0
197 C.H.	42	M	C	2	3d	N	S-P	2	1.0	Crisis	Chill following serum		>1.0	"	8	0
203 W.B.	21	M	W	1	5th	N	S-P	2	0.6	Crisis	0		0.1–0.1	"	2	0
209 S.W.	33	M	C	3	5th	10	S-T	8	0.6	Crisis	Empyema		>1.0	"	19	0

203 W.B.	21	M	W	1	5th	N	S-P	2	0.6	Crisis	0		0.1–0.1	"	2	0	
209 S.W.	33	M	C	3	5th	10	S-T	8	0.6	Crisis	Empyema		>1.0	"	19	0	

2. Cases treated with drug plus serum—more than 100,000 units

106 F.B.	49	M	W	2	3d	6	S-P	25	2.7	Lysis	Serum sickness, sterile pleural effusion, hematuria	Diabetes mellitus					
110 R.C.	27	M	C	2	7th	N	S-P	15	2.5	Crisis	Hematuria						
138 A.H.	42	M	C	3	5th	60	S-P	17	12.7	Lysis	Serum sickness, empyema	Azotemia	1.–3.	"	7		
147 H.M.	23	M	C	1	5th	N	S-P	9	3.7	Crisis	0						
167 M.McC.	35	M	C	5	11th	P	S-P	6	14.7	Crisis	Hematuria, relapse	Azotemia, alcoholic	>3.5	"	5		

3. Cases treated with serum alone

175 E.L.	21	F	C	1	3d	1			8.7	Lysis	0	0					

4. Cases treated with drug alone

157 L. J.	18	M	C	1	1st	N	S-T	2		Crisis	Sterile pleural effusion	Hematuria, congenital syphilis with hemiplegia					
59 L.B.	7	F	W	1	3d	N	S-T	2		Crisis							
65 E.D.	46	M	W	1	5th	P	S-P	3		Crisis							
113 J.M.	50	M	W	1	3d	N	S-P & S-T	9		Crisis							
124 E.K.	22	M	W	2	3d	N	S-P	12		Lysis	Relapse with spread	Nephritis					
126 H.G.	46	M	C	1	4th	5	S-P	7		Crisis	0						
161 W.W.	42	M	W	1	?	N	S-P	14		Lysis	0	Empyema on admission	>0.1	15+		0	
168 J. G.	22	M	C	1	3d	N	S-T & S-P	7		Lysis	0		0.001	7		0	
169 V.D.	69	F	W	1	?	N	S-T	9		Crisis	Spread when drug stopped	Debility and senility	0	0		0	
172 H.v.D.	26	M	W	3	6th	3	S-P	8		Crisis	Hematuria		>1.0	6		0.01	
195 C.D.	27	M	C	1	3d	N	S-T	4		Crisis	0		0.1	6		0	
206 N.T.	37	M	C	3	4th	500	S-T	9		Lysis	Drug fever and rash, empyema	Asthma	0.1	19		0	
210 D.L.	39	M	W	1	6th	N	S-T	8		Lysis	0						

N = negative, P = positive, figures indicate number of colonies per c.c. of blood culture. S-P = sulfapyridine, S-T = sulfathiazole.
Crisis indicates fall in temperature to 100°F or below rectally within 36 hours after treatment was started.
* Unless otherwise noted, figure indicates number of days after serum administration that antibody determinations were last made. Except for #181 all values on last day tested were undiminished from original level.
† Antibody titre fell to below 0.1 unit per c.c. after 8 days.

the plan of therapy had to be economical of time as far as the actual administration of serum was concerned. Consequently, it was decided to administer the whole amount of serum at one time. It is worthy of note that five cases received less than 100,000 units. By this means it was attempted to find out whether the quantity of serum might be safely reduced still further. The results of this phase of the work will appear in the section dealing with the results of the antibody studies.

The plan of therapy as finally evolved consisted in starting drug therapy at once. Then after a lapse of 3 or more hours, the whole

TABLE III

Results of treatment of Type I pneumonia

GROUP NO.	TEMPERATURE RESULT		BACTERE-MIC	COMPLICATIONS	DRUG REACTIONS	DRUG THERAPY CONTINUED
	Crisis	Lysis				
						days
1	18	2	3	Empyema, 2	6	4.4
2	3	2	3	Empyema, 1 Sterile pleural effusion, 1 Relapse, 1	3	14.4
3	0	1	1	0	0	—
4	8	5	4	Sterile pleural effusion, 1 Spread, 2 Empyema, 1	2	7.7
Total.....	29	10	11	9	11	

quantity of serum was administered at one time. Of the patients treated in this manner, 18 recovered by crisis, while 2 recovered by lysis. The drug therapy was continued for an average of 4.4 days in these cases as compared with 7.7 days in the Group 4 cases. Drug reactions were observed in 6 cases. Three cases were bacteremic. There were 4 cases of hematuria, as well as one case each of oliguria, and of fever. Of the 2 cases of empyema which were discovered in these patients, one was present on admission, while the other was strongly suspected (and was probably present) at that time, but no infected fluid was obtained for several days.

From the data presented (Table III), it may be seen that 11 or 28 per cent of the whole series of pneumonia patients were bacteremic on admission. In none of these cases were positive blood cultures obtained subsequently. Including the cases in Group 1, 4 cases of empyema were observed (10.3 per cent). Sterile pleural effusions were present in 4 cases also. One patient suffered a relapse after drug therapy was stopped, while in 2 cases a spread of the pneumonia occurred while the patients were still under treatment. Drug reactions occurred in 11 cases (28 per cent). Of these, hematuria was most frequently observed; it was seen 8 times (20 per cent). No deaths occurred in the series.

IMMUNOLOGICAL STUDIES

Four or five different kinds of antibody determinations were made in the majority of the cases which make up Group 1. The complete results for a single typical case (#130) are shown in Table IV. It seems impractical to detail the findings in all the other individual cases (Table V). The experience with the Francis skin test for following a course of therapy of this variety has been very disappointing. Although, on the basis of the protective antibody studies, it might have been expected that the test would have been quite satisfactory (18), the test itself became positive either too late to be of value, or else not at all. Nineteen patients were tested systematically. In only one of these was the test positive at a time when it was of definite value in determining the treatment of the case, in 5 the test was of questionable value, while in the remaining 13 patients the test was of absolutely no clinical significance. (This latter group included 3 "false positive" cases). Sera from 12 of the cases were tested for agglutinins microscopically. In one the test was equivocal throughout. In all the rest the test became strongly positive immediately after the administration of the serum, but in 6 of these 11 the test rapidly became less strongly positive in the course of the next few days, so that sera collected several days after serum administration showed a marked falling off of agglutinating power. On the other hand, the "thread" test, which gave almost identical immediate results in the sera of the 15 patients tested in this way, remained fairly strongly positive as long as the tests were done (for about 6 days sub-

TABLE IV

Antibody determinations—case # 130

DATE	SKIN TEST (SSS)	AGGLUTINATION		"THREAD" TEST		MOUSE PROTECTION	PRECIPITIN
		1-5	Last + Tube	1-5	Last + Tube		
						units/c.c.	
2/13*	0	0	0	±	0	<0.002	0
2/14	0	++++	1/10	++	1/80	>0.7	
2/15	0	++++	1/10	?	1/20	0.1	+++
2/17	0	++	1/5	++	1/10	>0.7	
2/19	0	++	1/5	+++	1/20	>0.7	++
2/21	±	±	1/5	++	1/20	>0.7	++
2/23	+					>0.7	

* Before treatment.

TABLE V

Comparison of results of tests for antibodies—Group I

CASE NO.	SKIN TEST			AGGLUTINATION*	"THREAD" TEST*	MOUSE PROTECTION
		Day of Treatment	Day of Disease			
						units/c.c.
35	+	Before	4	+	1/16	0.1–1.0
40	+	4	6		1/32	0.1–1.0
52	+	9	12	1/2	1/20	>0.7
53	+	5	7	1/5	1/80	>0.7
79	+	Before	8	1/10	1/80	>0.7
84	+	1	3	1/20	1/80	>0.7†
90	+	Before	2	1/20 ↓	1/20	>0.7
94	+	2	6	1/2 ↓	1/80	>0.7
96	0	8	10	1/10 ↓	1/20 ↓	>0.7
107	+	4	6			
127	+	5	7			>1.0
129				1/10 ↓	1/80	>1.0
130	+	9	16	1/10 ↓	1/80	>0.7
135	0	2	2	1/5 ↓	1/10	>0.7
156	+	4	6	1/5	1/10	>0.7
181	+	5	7		1/8	1.0 ↓
189	+	Before	3			>1.0
197	+	3	5			>1.0
203	+	3	7		1/20	0.1–1.0
209						0.1–1.0

↓ = Antibody titre decreased in subsequent tests (see text).

* Figures indicate highest dilution to give a positive test.

† Before treatment.

sequent to serum administration, in the average case). In only one case was any appreciable diminution in the titre noted. A few precipitin tests were performed on samples of serum from these cases, and, as might have been anticipated, they were all strongly positive after the serum had been given.

Mouse protection tests were performed on the sera from 19 of the 20 patients in Group 1. The results of these tests have been recorded in Tables II and V. It may be seen that in every case the value of the protective antibodies attained a significant level immediately after serum administration, and maintained that level as long as tests were performed. The only exception was case #181, a colored female who developed lobar pneumonia 2 days post-partum and was admitted in the third day of her acute illness. On admission she had an already established empyema, as well as a positive blood culture. In this one instance the antibody titre fell below 0.1 unit per c.c. of patient's serum 8 days after treatment had been instituted. Nevertheless, her recovery was uneventful after a rib resection had been performed in order to establish adequate drainage of the empyema. It should be noted that 15 of the 19 cases showed titres which are recorded as "greater than 0.7 or 1.0 units per c.c." It may be that the actual value attained was considerably higher than 1.0 unit and that that fact is responsible for the well sustained level of antibodies. No tests were performed to investigate the validity of this assumption, however.

As far as concerns the other groups of patients, no definite program of antibody determinations of any kind was carried on, save for the precipitin tests and their controls (mouse protection, "thread" and specific polysaccharide skin tests) in 7 cases of Group 4. To these were added studies of 2 cases of type II pneumonia. Seven out of 9 of these developed demonstrable precipitins between the sixth and fifteenth day of disease. Mouse protective tests and "thread" tests also showed a rise in antibodies at about the same time. These observations were made using 1–10,000 and 1–20,000 dilutions of Felton's specific polysaccharide. The results were less constant and more difficult of interpretation when a 1–50,000 solution of the capsular substance was employed, for only 2 cases showed inconstant, weakly positive precipitation at this dilution.

DISCUSSION

In 1931 Felton (19) compared several different types of antibody determination with the then recently standardized mouse protection antibody test. At that time he believed that the estimation of nitrogen precipitible by specific polysaccharide was probably the only test which was sufficiently accurate to compare closely with the mouse protection test. In the present study the Francis skin test has been of little practical value. There can be little question of the extremely important part that that test plays in the therapeutic control of pneumonias which are treated entirely with type specific serum (17), but it seems evident that the test cannot be relied on in such a scheme of treatment as has just been described. Perhaps the explanation of the failure of this test may be that there is never a quantity of antibody circulating which is sufficiently in excess of the capsular polysaccharide to permit the test to become positive. As for the microscopic agglutination and the "thread" tests, it would appear that these tests became positive sufficiently often to parallel closely the findings with the mouse protection test. In this respect they may be considered to be of significance in evaluating the effectiveness of therapy. Furthermore, it would seem that the "thread" test remained positive longer and so might well be classed as being somewhat more accurate than its companion method. No false positives were encountered with either of these tests, and in this respect they were far superior to the Francis skin test which in this series was found to be positive in 15 per cent of the cases before any therapy had been inaugurated. Despite the rather great expense which it entails, the determination of mouse protective antibodies is widely regarded as the most satisfactory single antibody test available at this time. Discussion has arisen recently as to the possibility of deriving a regression curve from which a table of relationship for these two methods could be evolved. By means of this table Heidelberger's test for the nitrogen precipitible by the specific capsular polysaccharide might be used instead of the more expensive, cumbersome mouse method. The results so obtained could then be interpreted from the table in terms of mouse protective antibody units. From a statistical point of view the results so obtained might be so adjusted as to be much more accurate than those results obtained by using

groups of 5 mice (20). Despite the potentialities of other methods, at present the protective antibody test is the only method available which can be standardized in practical terms of units.

A search of reports which have appeared in the literature concerning the serum therapy of type I pneumonia, has failed to reveal any definite information concerning the fate of the protective antibodies in the intervals between repeated doses of serum in individual patients. It was shown by Cole in 1917 (21), by means of the agglutination reaction, that the agglutinin titre rose promptly after the administration of a sub-effective amount of serum, only to fall in a few hours if no more serum were injected. The only reference to the fate of protective antibodies is that of Park and Cooper in their discussion of the frequency of injecting serum (22). "How frequently should an injection be repeated? This depends on the amount of soluble toxic substance being formed or already formed. The quantity of toxic substance influences the persistence of the horse antibodies in the body of the pneumonia patient. This we have tested both in healthy persons and in those suffering from pneumonia. When sufficient time has elapsed after an intravenous injection for the dispersion of the antibodies throughout the fluids of the body, it is found that they are fairly stable in normal persons. The quantity in the blood diminishes gradually so that at the end of the day from one-half to three-fourths is lost. With each successive intravenous dose the amount rises and then falls again. In toxic cases of pneumonia the conditions are quite different; the antibody matching the type of pneumococcus causing the pneumonia is quickly, partly or wholly neutralized by the specific soluble substance, while the antibodies in polyvalent serums specific for the two other types are only slightly affected and decline slowly as in a normal person." Wood (18) showed the same thing in a different way with the Francis skin test. In cases treated with a polyvalent serum, it took only 5,000–10,000 units to bring the skin test into strong and persistent positivity for the unnecessary type, whereas it took very much larger doses of the serum to make the necessary type persistently positive.

At the start of these studies it was thought that following a sub-effective dose of serum one particular test for antibody might become positive during the period of the clinical recovery of the patient.

In this way it was hoped that some insight might be gained into the mechanism by which these pneumonia patients recovered from their illness. This hope was not realized. As has been stated above, the antibody titres rose immediately and remained elevated, almost without exception, as long as the patient's sera were tested. An explanation of this phenomenon, which would also account for the advantage enjoyed experimentally by mice treated with drug before serum, was that, when the patient was given his drug shortly after admission, the organisms were prevented from further growth and elaboration of polysaccharide. Later, when the type-specific serum was administered, that quantity of serum was sufficient to neutralize the circulating specific soluble substance and at the same time to provide an excess of circulating antibody for the individual until such a time as he was able to manufacture his own antibodies. Such an hypothesis would seem to fit the observed facts quite satisfactorily.

In a limited fashion certain additional data have been accumulated concerning the time of appearance of immune substances in cases of pneumonia treated with drug alone. Excellent studies by Edwards (23), Finland (24) and Wood (7), have seemed to show that antibodies appear in these cases at about the same time as would be expected in a naturally recovering (untreated) pneumonia. This work with mouse protective antibodies and with agglutinins was further substantiated by the use of the "thread" test (25). Recently Kneeland and Mulliken (10) by using the precipitin test have come to the conclusion that the appearance of antibodies is retarded by the drug treatment of pneumonia. The several cases of this present series which were studied with this problem in mind failed to confirm the work of these latter investigators. The results set down here suggest, however, that positive results are easier of interpretation if lower dilutions of specific soluble substance are used.

It would appear that there are very definite practical implications to the results obtained in the treatment of this group of patients. The preferred method of therapy in pneumococcal pneumonia would seem to be to administer sulfapyridine or sulfathiazole to the patient for a period of several hours, then to give type-specific serum. After 24–36 hours of normal temperature the drug administration may be

discontinued. In all but the most severely ill patients a single dose of 100,000 units of serum would appear to be sufficient, although in many cases probably 50,000–60,000 units would be ample, for the antibody determinations made on patients treated with these smaller doses seemed to rise to almost as effective titres as in those treated with the larger amount. In general, it would seem safe to stop the drug on the second day of normal temperature because the patients maintain sufficient circulating antibody to protect themselves. These patients seemed to do just as well as those who were treated for a longer period, their antibodies persisted at as high a level, and in none of them was any relapse noted. From the records of this small series it is difficult to reach any definite conclusions as to the frequency of complications when drug and serum therapy are employed in combination.

SUMMARY AND CONCLUSIONS

1. A group of 39 treated type I pneumococcal pneumonias without a death is reported. Eleven cases had positive blood cultures. Twenty of these patients received either sulfapyridine or sulfathiazole and 100,000 units or less of type-specific anti-serum, 6 received one of these compounds and more than 100,000 units of serum, 1 received serum alone, while 13 received only drug therapy.

2. The experimental data suggest that therapy with the combination of drug and serum is superior to treatment with either alone. Treatment appeared to be more efficacious if drug therapy precedes serum therapy by several hours, than if serum is administered first.

3. Immunological studies in patients treated with combined therapy in the manner described above, show that the patient's serum tends to maintain an effective level of antibody without further injection of antibody.

4. Evidence is presented to show that antibody appearance time is not delayed when pneumococcal pneumonia is under drug therapy alone.

5. On the basis of the experience reported here the preferred scheme of therapy for pneumococcal pneumonia would appear to be immediate administration of a drug. From one to several hours later 100,000 units of type-specific serum should be given in a single in-

jection. Drug treatment should be continued until the temperature has remained normal for 24–36 hours.

The sulfathiazole used in this study was furnished through the courtesy of E. R. Squibb and Sons.

Dr. Lloyd Felton very kindly provided a virulent strain of type I pneumococcus and the polysaccharide used in this study.

The writer is greatly indebted to Mr. Earl Ott for very considerable technical assistance in carrying out these studies.

BIBLIOGRAPHY

1. Brown, T. M.: Protective Action of Sulfanilamide and Anti-Meningococcus Serum on Meningococcus Infections of Mice. *Bull. Johns Hopkins Hosp.*, 1937, **61:** 272.
2. Branham, S. E., and Rosenthal, S. M.: Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice. *Pub. Health Rep.*, 1937, **52:** 685.
3. Callomon, V. B.: Treatment of Pneumonia with Type-Specific Immune Rabbit Serum. *Am. J. Med. Sci.*, 1939, **198:** 349.
4. Marshall, E. K., Jr., and Long, P. H.: The Intravenous Use of Sodium Sulfapyridine. *J. A. M. A.*, 1939, **112:** 1671.
5. Wood, W. B., Jr.: The Clinical Application of the Francis Skin Test. *J. Clin. Invest.*, 1940, **19:** 105.
6. Felton, L. D.: Variables in Mouse Protection Test of Anti-Pneumococcus Serum. *J. Immunol.*, 1930, **19:** 485.
7. Wood, W. B., Jr., and Long, P. H.: The Mechanism of Recovery from Pneumococcal Pneumonia in Patients Treated with Sulfapyridine. *Ann. Int. Med.*, 1939, **13:** 612.
8. Sabin, A. B.: The Microscopic Agglutination Test in Pneumonia. *J. Infect. Dis.*, 1930, **46:** 469.
9. Paul, J. R.: Pneumococcus Variants. *J. Bact.*, 1934, **28:** 45.
10. Kneeland, Y., Jr., and Mulliken, B.: Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfapyridine. *J. Clin. Invest.*, 1940, **19:** 307.
11. Powell, H. M., and Jamieson, W. A.: Combined Immuno and Chemotherapy of Pneumococcus Rat Infections. *J. Immunol.*, 1939, **36:** 459 (also *Proc. Soc. Exp. Biol. and Med.*, 1939, **41:** 281).
12. Bullowa, J. G. M.: The Specific Therapy of the Pneumonias. I. The Choice of a Remedy. *J. Mich. St. Med. Soc.*, 1939, **38:** 563.
13. Finland, M., and Dowling, H. F.: Dose of Antibody Effective in Treatment of Pneumococcus Type II Pneumonia. *Am. J. Med. Sci.*, 1936, **191:** 658.
14. MacLeod, C. M., Hoagland, C. L., and Beeson, P. B.: The Use of the Skin Test with Type Specific Polysaccharides in the Control of Serum Dosage in Pneumococcal Pneumonia. *J. Clin. Invest.*, 1938, **17:** 739.

15. Wood, W. B., Jr.: Treatment of Pneumococcic Pneumonia. *J. A. M. A.*, 1939, **113:** 745.
16. Loughlin, E. H., Bennett, R. H., and Spitz, S. H.: The Treatment of Lobar Pneumonia with Rabbit Anti-Pneumococcus Serum. *Ibid.*, 1938, **111:** 497.
17. Blake, F. G.: *Personal Communication.*
18. Wood, W. B., Jr.: A Study of the Mechanism of the Skin Reaction to Type Specific Polysaccharide. *J. Clin. Invest.*, 1940, **19:** 95.
19. Felton, L. D.: The Correlation of Protective Value with the Titres of Other Antibodies in Type I Anti-Pneumococcus Serum. *J. Immunol.*, 1931, **21:** 341.
20. Reed, L. J.: *Personal Communication.*
21. Cole, R.: Neutralization of Anti-Pneumococcus Immune Bodies by Infected Exudates and Sera. *J. Exp. Med.*, 1917, **26:** 453.
22. Park, W. H., and Cooper, B.: Dosage and Administration of Serum in Pneumonia. *J. A. M. A.*, 1928, **90:** 1349.
23. Edwards, J. C., Kircher, T. E., Jr., and Thompson, L. D.: Effect of Sulfapyridine on Immune Response to Pneumococcal Infections. *Proc. Soc. Exp. Biol. and Med.*, 1939, **42:** 539.
24. Finland, M., Spring, W. C., Jr., and Lowell, F. C.: Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine. *J. Clin. Invest.*, 1940, **19:** 179.
25. Blake, F. G., and Haviland, J. W.: *Unpublished Data.*

THE EFFECT OF INSULIN ON GLYCOGEN DEPOSITION AND ON GLUCOSE UTILIZATION BY ISOLATED MUSCLES

CHALMERS L. GEMMILL AND LOUIS HAMMAN, JR.

From the Department of Physiology, The Johns Hopkins University, School of Medicine

Submitted for publication October 25, 1940

In a former publication, Gemmill (1) described an "in vitro" effect of insulin on the isolated diaphragm of the rat. In these experiments insulin was added to Ringer's solution containing glucose and buffered with phosphate. The action of the insulin produced a definite increment in the glycogen content of a muscle when it was shaken for three hours in this solution. These experiments have been repeated and extended by studying the effect of various concentrations of glucose on glycogen deposition, by determining the glucose utilization from the medium, and by testing other substrates in this reaction.

METHODS

The experiments were conducted in the same manner as in the former investigation (Gemmill, 1). For the insulin experiments, 1 ml. (40 units) of a solution of zinc insulin crystals (Lilly) was added to 49 ml. of Ringer's solution buffered with phosphate and containing glucose. Two ml. of this solution were placed in the Warburg flasks. Therefore, the tissue was in contact with 1.6 units of insulin. When glucose determinations were made, one ml. of the solution was removed from the flask at the end of the experiment; the proteins were precipitated by zinc hydroxide (Somogyi, 4) and the glucose was determined by the Shaffer-Somogyi method (3). Suitable control experiments were made for these determinations. These consisted in shaking the glucose solutions for three hours without any tissue being present. When the final values for glucose concentration were compared with the original ones no differences were observed. Therefore, the presence of muscle is necessary for the utilization of glucose.

In these experiments a muscle containing a small amount of glucose is added to a solution of large glucose concentration. This by itself would give an apparent glucose utilization. However, since all of these experiments were carried out by comparing a muscle in one flask with another in a separate vessel the dilution effect would be the same for both solutions.

RESULTS

The results are presented in Fig. 1 and in Tables 1, 2, and 3. In Fig. 1 the results for the glycogen determinations are expressed in terms of mgm. increments (as glucose) per 100 mgm. of wet weight

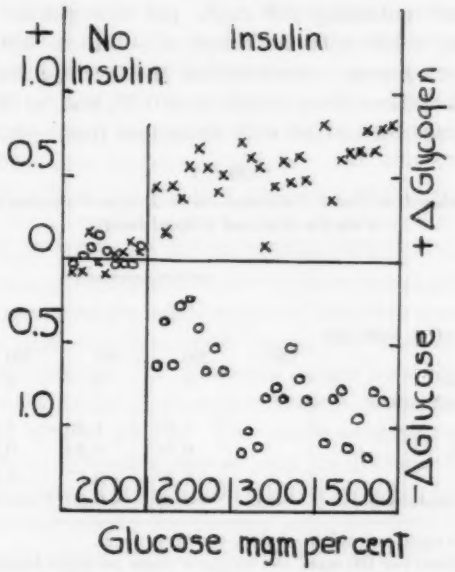


FIG. 1. DEPOSITION OF GLYCOGEN AND UTILIZATION OF GLUCOSE BY THE ISOLATED DIAPHRAGM WITH AND WITHOUT INSULIN

Glycogen deposition reported as increments (glucose) in mgm. per 100 mgm. of wet weight of tissue per 3 hours; glucose utilization as decrements in mgm. per 100 mgm. of wet weight of tissue per 3 hours. In the insulin experiments, 1.6 U were present in each vessel. Concentrations of glucose in the medium are given at the bottom of the figure.

of tissue per three hours. The glucose analyses are given in mgm. decrements per 100 mgm. of wet weight of tissue per three hours. It may be seen in the figure that the glycogen deposition increases slightly with increasing concentration of glucose under the influence of insulin. The average values of the increments in glycogen in mgm. per 100 mgm. of tissue with and without insulin are given in

Table 1. In the control experiments in which insulin was not present in the medium, there was very good agreement in the glycogen content of the two corresponding sections of the diaphragm. The average increment was +0.01 and the deviations for the increments between experiments were from −0.06 to +0.14. When insulin was present in the medium containing 200 mgm. per cent glucose the average increment was +0.45 with deviations of +0.16 to +0.66. At 300 mgm. per cent glucose concentration the average increment was +0.50 with deviations from +0.07 to +0.70; and, at 500 mgm. per cent, the average was +0.66 with deviations from +0.35 to +0.80.

TABLE 1

Summary of Experiments on Glucose Utilization and on Glycogen Formation by the Diaphragm of the Rat With and Without Insulin

	INSULIN EXPERIMENTS				CONTROL EXPERIMENTS
Glucose Concentration, mgm. per cent	100[4]	200	300	500	200
No. of experiments	5	9	9	8	9
Average glucose utilization:[1]					
With insulin		1.03	1.46	1.56	0.51[3]
Without insulin		0.54	0.59	0.70	0.48
Difference		−0.49	−0.87	−0.86	−0.03
Average glycogen deposition[2]	+0.12	+0.45	+0.50	+0.66	+0.01

[1] Mgm. per 100 mgm. wet weight of tissue per three hours.
[2] Mgm. (as glucose) per 100 mgm. wet weight of tissue per three hours.
[3] No insulin used in the control series.
[4] Results obtained in previous experiments (Gemmill, 1).

The average result of final experiments from the former series (Gemmill, 1) in which the concentration of glucose was 100 mgm. per cent is included in the table. The average increment in that series was +0.12. The general trend was for a greater deposition of glycogen when the concentrations of glucose were increased in the medium, the amount of insulin remaining constant in all solutions. No detailed study has yet been made to determine whether the different concentrations of glucose affect the storage of glycogen "in vitro" in the absence of insulin.

The effect on glucose utilization obtained by varying the glucose concentrations in the medium in the presence of insulin, was more

striking than the effect on glycogen deposition. The average glucose utilization at 200 mgm. per cent concentration was 0.49 mgm. per 100 mgm. of tissue per 3 hours. Increasing the concentration to 300 mgm. per cent raised the average utilization to 0.87 whereas an additional increase in concentration to 500 mgm. per cent did not change the average utilization (0.86). The comparison between the average glycogen deposition and glucose utilization is of interest. At 200 mgm. per cent, there was good agreement between the glucose used from the solution and the glycogen deposited. The differences between these two values became greater with the increasing concentrations of glucose in the solution (Table 1). The utilization of glucose by the muscles which had not been subjected to the action of insulin was augmented by increasing the amount of glucose in the medium.

The two main pathways for the utilization of glucose by muscle are deposition as glycogen and oxidation to carbon dioxide and water. In order to determine the relative rôle of these two processes oxygen consumption determinations were made with and without insulin present in the medium. No marked changes were observed in the oxygen utilization of the diaphragm at various glucose concentrations, either with or without insulin. The results of these experiments are given in Table 2. At 500 mgm. per cent the average oxygen concentration of this tissue without insulin was 1.06 $mm.^3$ per mgm. of tissue per hour, but with insulin the average value was 0.93. These values are slightly higher than those reported in the former series at 200 mgm. per cent glucose. In this series the value of the controls (without insulin) was 0.93 whereas the average (with insulin) was 0.84. It is of interest to note that the average value obtained in the present series when neither insulin nor glucose were present, was of the same order of magnitude (0.93) as the values obtained when both of these variables were present. Since the results with and without insulin at 500 mgm. per cent agreed with those observed at 200 mgm. per cent, no determinations were made at 300 mgm. per cent. These results demonstrate that insulin does not augment the oxidation of carbohydrate to a degree that demands extra oxygen consumption. There may be, however, a slight isocaloric shift of metabolism from fat combustion to carbohydrate which would be undetected in these experiments.

The fact remains that more glucose disappeared from the medium at 300 and 500 mgm. per cent concentrations than could be accounted for by glycogen deposition or by oxidation. This small difference may be explained by assuming the formation of intermediates between glucose and glycogen in the muscle.

TABLE 2

Oxygen Utilization by the Isolated Diaphragm of the Rat With and Without Insulin

GLUCOSE CONCENTRATION	INSULIN 1.6 U IN 2 ML. OF RINGER'S SOLUTION	TIME OF EXPERIMENT	O_2 UTILIZATION	WEIGHT OF TISSUE
mgm. per cent		*hours*	*mm.³ per mgm. wet weight per hour*	*mgm.*
0	−	1	0.91	97
0	−	3	0.93	127
0	−	3	0.95	137
		Average	0.93	
200	−	3	0.93	146
500	−	1	1.00	187
500	−	1	0.97	202
500	−	3	0.84	240
500	−	3	0.99	136
500	−	3	1.33	150
500	−	3	1.35	130
		Average	1.06	
500	+	3	0.74	155
500	+	3	0.78	240
500	+	3	0.78	138
500	+	3	1.10	101
500	+	3	0.90	142
500	+	3	1.25	135
		Average	0.93	

Various additional substrates besides glucose were tested in order to determine if they formed glycogen and if insulin accelerated this reaction. The substrates used were d-galactose, d-levulose, l-xylose, d-arabinose, maltose, succinate, lactate and citrate.

Several experiments were made with each of the different substrates. In the first, a comparison was made between the glycogen content of two corresponding muscles without insulin being present in order to determine whether the substance under study formed glycogen "in

TABLE 3

The Effect of Various Substrates on Glycogen Deposition in the Isolated Diaphragm of the Rat

SUBSTRATE	CONCENTRATION	GLYCOGEN CONCENTRATION (AS GLUCOSE)				
		1 Without Substrate	2 With Substrate	3 Substrate with Insulin	Differences Column 2-1	Differences Column 3-2
	mgm. per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
d-Galactose (Eastman)	200	0.29	0.39		+0.10	
			0.52	0.58		+0.06
			0.38	0.48		+0.10
d-Levulose (Pfanstiehl)	200	0.46	0.50		+0.04	
			0.52	0.51		−0.01
			0.80	0.90		+0.10
l-Xylose (Eastman)	200	0.25	0.24		−0.01	
			0.31	0.39		+0.08
d-Arabinose (Eastman)	200	0.26	0.35		+0.09	
			0.40	0.43		+0.03
			0.46	0.40		−0.06
Maltose (Eastman)	200		0.48	0.48		0.00
			0.60	0.64		+0.04
Sodium succinate (Eastman)	200	0.58	0.58		0.00	
			0.42	0.38		−0.04
			0.19	0.20		+0.01
Sodium lactate[1]	200	0.46	0.38		−0.08	
			0.42	0.45		+0.03
			0.49	0.33		−0.16
Sodium citrate (Baker)	200	0.29	0.28		−0.01	
			0.31	0.34		+0.03
			0.25	0.27		+0.02
Glucose (Pfanstiehl)[2]	200		0.50	0.95		+0.45

[1] Prepared from zinc lactate (Eastman).

[2] Results from Table 1; average of nine experiments.

vitro." In the other determinations, insulin was added to the medium in order to see whether this hormone aided in the conversion of the material to glycogen. The results of these experiments are given

in Table 3. The largest increment observed in any of these experiments was +0.10 which was within the deviations observed in the control series without insulin. Therefore, under the conditions of our experiments, none of the substrates studied formed glycogen either with or without the presence of insulin.

DISCUSSION OF RESULTS

These results demonstrate that insulin accelerates the deposition of glycogen in the muscle from glucose in the medium. A discussion of the literature on this subject is given in the former paper (Gemmill, 1). These experiments show also that the utilization of glucose depends on the concentration of glucose in the surrounding medium. A similar conclusion was reached by Wierzuchowski (6) and Soskin and Levine (5) from calculations of glucose utilization in the intact animal and by Lundsgaard, Nielsen, and Ørskov (2) from perfusion experiments. The "in vitro" insulin deposition of glycogen in muscle requires glucose as its substrate since the results for numerous other compounds were negative. Insulin, while accelerating the utilization of glucose, does not increase the consumption of oxygen by the isolated muscle. Under the conditions of our experiments, therefore, the main function of insulin is to aid the deposition of glycogen in the muscle from glucose in the medium.

SUMMARY

The demonstration of an "in vitro" effect of insulin on the deposition of glycogen in the isolated diaphragm of the rat has been repeated and the experiments have been extended. Insulin aids in the deposition of glycogen from glucose in this reaction. This phenomenon is not associated with an increased oxygen consumption. The amount of glucose utilization and of glycogen deposition depends on the concentration of glucose in the medium. Galactose, levulose, xylose, arabinose, maltose, succinate, lactate or citrate do not act as substitutes for glucose in this reaction.

REFERENCES

(1) Gemmill, C. L.: The effect of insulin on the glycogen content of isolated muscles. *Bull. Johns Hopkins Hosp.*, **66**, 232, 1940.

(2) LUNDSGAARD, E., N. A. NIELSEN AND S. L. ØRSKOV: On the utilization of glucose and the formation of lactic acid in the isolated hind limb preparation. *Skand. Arch. f. Physiol.*, **81**, 20, 1939.

(3) SHAFFER, P. A. AND M. SOMOGYI: Copper-iodometric reagents for sugar determination. *J. Biol. Chem.*, **100**, 695, 1933.

(4) SOMOGYI, M.: A method for the preparation of blood filtrates for the determination of sugar. *J. Biol. Chem.*, **86**, 655, 1930.

(5) SOSKIN, S. AND R. LEVINE: A relationship between the blood sugar level and the rate of sugar utilization affecting the theories of diabetes. *Amer. Journ. Physiol.*, **120**, 761, 1937.

(6) WIERZUCHOWSKI, M.: Oxidation of glucose as function of its supply. *Journ. Physiol.*, **90**, 440, 1937.

NEUROTROPISM AND THE GENESIS OF CEREBRAL LESIONS IN POLIOMYELITIS: AN EXPERIMENTAL STUDY[1]

DAVID BODIAN[2] AND HOWARD A. HOWE

From the Department of Anatomy, Johns Hopkins Medical School

Submitted for publication October 18, 1940

The neuronal destruction in poliomyelitis, although of special interest because of its primary role in the symptomatology of this disease, is, as is well known, only a small part of the cellular reactions which occur in the central nervous system as the result of virus invasion. It is now generally held that the neuronal damage occurs by direct action of the virus on the nerve cell, but opinions are divergent as to the primary factors involved in the mobilization and reaction of the enormous numbers of neuroglial and inflammatory cells which constitute the principal cellular components of the characteristic proliferative lesions in the nervous system. That the injury response of the neurones to virus invasion may occur without the reaction of non-neuronal elements, is recognized by most workers (1, 2, 3, 4, 5, 6, 7, 8, 9), but on the other hand it is frequently affirmed that non-neuronal elements, microglial or leucocytic in origin, may also be mobilized in the absence of observable changes in the neurones of the region concerned (8, 9, 10). The latter phenomenon is taken to indicate a possible direct action of the virus in inducing the "mesodermal-glial" response. Obviously, in the absence of critical evidence to the contrary, it may equally well be assumed that the mesodermal-glial response is secondary to some sort of reaction of the nerve cells to the virus, whether such reaction is observable microscopically as such or not. It is evident that the point at issue is a critical one for an understanding of the pathogenesis of this disease as a nervous disease, but in spite of the abundance of data available from studies in man and in the experimental animal, it has not been possible to

[1] Aided by a grant from the Commonwealth Fund.

[2] Now of the Department of Anatomy, Western Reserve University, School of Medicine.

assert positively either that the virus of poliomyelitis is strictly "neuronotropic" in its behavior, that is, has a selective affinity for, and perhaps is dependent for its growth upon, living nerve cells, or whether it is merely "neurotropic" in the sense of Hurst (7), that is, has a predilection for nervous tissues, including neuronal and non-neuronal elements. Although presumptive evidence from histopathological studies is not lacking, it has failed to resolve this problem, as can be judged by the various interpretations placed upon the findings in ordinary pathological material by many competent workers.

The primary difficulty inherent in this problem is that of dissociating the reaction of neuronal elements from that of neuroglial and mesodermal infiltrative elements in the central nervous system, in which both the former and the latter elements, so different in their structure, functions, and metabolism, are nevertheless so intimately intermingled. The experiments to be described in this report have been designed to separate the non-neuronal elements from the nerve cells in their reactions to virus, by taking advantage of a well-known neuropathological phenomenon, namely, retrograde degeneration of nerve cells in the optic thalamus after injury to their cortical axonal terminals (Nissl). This degeneration of nerve cells leaves a virus-susceptible region of the nervous system almost completely destitute of neurones without diminishing the numbers of neuroglia or significantly altering the blood supply. In some regions of the thalamus a gliosis occurs coincident with, or following, the degeneration of the nerve cells, but this gliosis is invariably diffuse and cannot be mistaken for the focal glial accumulations which may occur in poliomyelitis.

It was previously reported (Bodian and Howe (11)) that in such regions of the thalamus as have undergone retrograde neuronal degeneration previous to infection with the virus of poliomyelitis, no lesions of any sort are found. Although this phenomenon strongly suggested that it was the absence of neurones which determined the absence of lesions, the possibility also presented itself that because of coincident degeneration of the axonal connections of the degenerated region of the thalamus with the projection region of the cerebral cortex, no virus or only a sub-infective quantity of virus could reach the thalamus and consequently no pathological response occurred. This was especially considered because of other evidence that infection

of the ventrolateral nuclei of the thalamus occurs primarily, although perhaps not exclusively, by spread from the corresponding projection area in the cerebral cortex. It was hoped, however, that by inoculating the virus directly into a region of retrograde degeneration it would be possible to study more critically the effect of the virus on non-neuronal elements in the absence of most of the neurones normally present.

It was the object of this study to determine by this method whether or not a cellular pathological response to the virus can occur in a susceptible nervous center in the absence of nerve cells, that is, by the direct action of the virus on non-neuronal elements of the nervous tissue. The presence of lesions of neuroglial or inflammatory origin in a region almost denuded of nerve cells, after direct virus inoculaton, in quantity equal to or greater than that found in a control thalamus would demonstrate that the mesodermal-glial response to virus is not dependent upon the presence of nerve cells. On the other hand, a significant diminution or absence of such lesions in a neurone-denuded region after direct virus inoculation would strongly suggest that the mesodermal-glial response depends on a chemotactic resultant of a virus-neurone reaction. As a matter of fact, it has been found that after direct inoculation of potent virus into such regions as the thalamus, the mesodermal-glial response is greatly reduced as compared with that in a normal region of the thalamus. This seems to be the case in spite of the fact that it has been shown that usually a complete degeneration of all nerve cells does not occur in the thalamus after cortical lesions, even after hemi-decortication (Walker (12)), but that scattered residual cells remain even in centers most severely involved. The findings and their interpretation will now be considered in detail.

EXPERIMENT 1 (A-50)

Young male rhesus monkey; incomplete left hemidecortication; inoculation of virus into left thalamus, after one month

October 23, 1939. An extensive left-sided craniotomy was performed. The cortical veins connecting with the longitudinal sinus were ligated and the left frontal and parietal lobes removed in one block, along with a large part of the temporal lobe. The animal had an uneventful convalescence.

November 22, 1939. The left cerebrum was re-exposed. Inoculations with straight needle of 0.05 c.c. of MV virus suspension were made into the depths of the ventro-lateral nuclear group. Three such inoculations were directed into the rostral, medial, and caudal parts of the thalamus respectively. The caudalmost inoculation was directed towards the lateral geniculate body. The following morning the animal was sitting up and eating ravenously. He exhibited a right hemiplegia, but also had definite weakness of the left leg, with accentuated deep reflexes.

November 25, 1939. Fever was noted on this day and on the following day.

November 27, 1939. The animal was found almost completely paralysed in the trunk and extremities, although the muscles of the eyes, jaws, face, and tongue were active. The paralyses of the extremities and trunk were flaccid and all deep reflexes were absent; only the tail was spared. Under ether anesthesia the animal was perfused through the aorta with two liters of 10 per cent neutral formalin containing 1 per cent acetic acid. After fixation and embedding in celloidin, serial sections were prepared of the entire brain and stained alternately by the gallocyanin method of Einarson, and with toluidin blue.

Histological Examination

Extent of operative ablation. The sections showed the following damage to the left cerebral hemisphere produced at operation, confirming the findings of gross inspection of the brain. The left frontal pole was almost completely removed with the exception of the medial and caudal parts of the orbital region and the gyrus rectus, which were spared. The parietal lobe was entirely absent. The rostral tip of the temporal pole, the superior temporal gyrus, and the superior half of the inferior temporal gyrus were destroyed, but the rest of the temporal lobe, including the gyrus hippocampi, amygdala, and hippocampus, was spared. The rostral half of the lateral portion of the occipital pole was destroyed, but the caudal and medial portions were intact. The corona radiata and the superior horizontal and vertical limbs of the optic radiation were also destroyed. The corpus striatum was largely spared, except for the rostral tip of the caudate nucleus and the claustrum. The preoptic and septal regions, and the diencephalon, were undisturbed.

On the right side the cerebral hemisphere was largely intact, except for softening of the gyrus cinguli and marginal gyrus from a point just rostral to the central sulcus back to the splenium of the corpus callosum. There were also small softenings confined to the leg region of the precentral and postcentral gyri.

Retrograde degeneration. In the left thalamus there was severe retrograde degeneration in most of the ventrolateral nuclear group, with the exception of the nucleus ventralis anterior, the peripheral margin of the pulvinar, the reticular nucleus, and the lateral portion of the lateral geniculate body. The anterior nuclear group also showed severe degeneration with, however, numerous residual cells in the nucleus anterior dorsalis and the nucleus anterior medialis. The medial, laminary, and mid-line nuclei were largely intact, except for the nucleus medialis dorsalis which was completely degenerated. In the nuclei showing severe retrograde degeneration most of the neurones normally present had disappeared, but scattered residual neurones, often showing signs of atrophy, and often staining poorly, could be found upon close inspection. These cells were especially numerous in the rostral part of the nucleus ventralis lateralis and in the anterior nuclear group.

On the right side there was retrograde degeneration only in the lateral part of the nucleus ventralis lateralis, corresponding with the softened area in the leg region around the central sulcus (Walker (12)), and in the nucleus anterior ventralis.

Inoculations and poliomyelitic lesions. All three inoculations had been placed in the left ventrolateral nuclear mass, with the most caudal one entering the lateral geniculate body and the optic tract. The inoculations had injured the left thalamus only along the needle tracks, and there was no evidence of traumatic hemorrhage or softening in this region.

When sections of the thalamus were examined, there was apparent at once a striking difference in the distribution of poliomyelitic lesions on the two sides. There was a great preponderance of perivascular and focal infiltrative lesions in the undegenerated nuclei of the right side (figs. 1 and 3), whereas the nuclei on the left side which showed severe retrograde degeneration, and in which the virus had been directly placed, showed remarkably few lesions (figs. 1 and 2). The lesions in the left thalamus were numerous in the nuclei of the internal medullary lamina and the midline, in the nucleus ventralis anterior, and in the nucleus centrum medianum, all of which showed no retrograde degeneration (figs. 1 and 2). In the severely degenerated ventrolateral nuclear mass, lesions were largely restricted to the periphery

of the inocula, and to small islands of residual cells in the degenerated areas. Large areas in which practically all neurones had degenerated, showed no poliomyelitic lesions of any kind, not even perivascular cuffing, although such lesions were abundant in the corresponding undegenerated region of the opposite side (figs. 1 and 3).

The left lateral geniculate body, in which the medial half or more showed severe retrograde degeneration, was the site of the most caudal inoculation. In view of the apparently great resistance of this center to the virus of poliomyelitis, previously reported (Bodian and Howe (11)), it was interesting to note the effect of direct inoculation of a highly concentrated virus suspension within its substance. No effect of the virus on the cells in the undegenerated portion of the nucleus was noted, and no focal infiltrative lesions were seen either in this part of the nucleus or in that part showing retrograde degeneration. Perivascular cuffing of a light degree was present however in this nucleus along the needle track containing the virus suspension.

Numerous heavy focal and perivascular mononuclear infiltrations were present in the right motor cortex, and in the hypothalamus and midbrain of both sides, as well as in the hindbrain. There were especially numerous and large lesions in the subthalamus and midbrain of the left side, adjoining the most caudal thalamic inoculation.

Summary of Experiment 1. Retrograde degeneration of most of the nerve cells in the left ventrolateral thalamic nuclear mass was caused by ablation of their projection center in the cerebral cortex. One month later, an emulsion of spinal cord containing potent poliomyelitis virus was inoculated directly into this susceptible region of the brain which had been denuded of nerve cells, but which was otherwise relatively normal. Although poliomyelitis occurred after five days, with typical pathological changes in the brain and spinal cord, lesions were practically absent in that portion of the left thalamus which had undergone previous retrograde nerve cell degeneration. This occurred despite the fact that the virus had been placed directly into the substance of this region. Such a result suggests that the characteristic response of the mesodermal-glial tissues in poliomyelitis, responsible for the non-neuronal lesions, does not depend on the presence of virus alone but rather is due to a resultant, perhaps chemotactic, of a virus-neurone reaction. This interpretation seems to be

confirmed by the finding that a minimal amount of inflammatory reaction is usually present in the immediate vicinity of the inoculum, regardless of whether or not the inoculated center shows any other lesions as is the case in the highly resistant lateral geniculate body. It is hardly surprising that this should be, since it may be assumed that the inoculum contains not only the virus, but also the nerve cells of the spinal cord and the products of their reaction with the virus.

EXPERIMENT 2 (993)

Young adult male rhesus monkey; left hemi-decortication; inoculation of virus into left thalamus

November 22, 1939. The left cerebral hemisphere was exposed, the sinus connections ligated, and the entire hemisphere dissected away in a single block, with care not to injure the underlying basal ganglia. Seven inoculations of 0.05 c.c. of MV virus suspension were made into the left thalamus and caudate nucleus with a straight needle.

November 23, 1939. The animal showed a complete right hemiplegia and a depressed temperature (97°C.—rectal), which subsequently reached a peak of 103.8° on November 26, and dropped again on November 27, when a flaccid paralysis of the left arm was noted. The animal's condition deteriorated rapidly and tube feeding was necessary.

November 28, 1939. The animal was found dead. It was estimated that he had died not more than six hours previously. The brain was removed, appeared to be in excellent condition, and was fixed by immersion in 10 per cent formol containing 1 per cent acetic acid.

Histological Examination

Extent of operative ablation. On the left side almost the entire cerebral cortex was destroyed. Only the gyrus rectus, a medial strip of the inferior temporal gyrus, the gyrus hippocampi, and the hippocampus were preserved. The amygdala and other striatal centers were also intact.

The right cerebral hemisphere was the site of an extensive softening, involving the entire gyrus cinguli and the gyrus marginalis, and extending laterally over the dorsal surface of the hemisphere for a distance of about 8 mm. and to a depth of 4 mm.

Retrograde degeneration. Since a period of only six days had elapsed between operation and time of death of this animal, it was not to be expected that severe retrograde degeneration would occur. It was

hoped that this experiment would show the reaction to virus of nerve cells in the earliest stages of retrograde cell change. Very little, if any, diminution of nerve cells was found in the thalamus as a consequence of retrograde degeneration. There was evident only a markedly pale staining reaction of most of the cells in the left ventrolateral nuclear mass, in the nucleus medialis dorsalis, and in the anterior nuclear group. No evidence of retrograde cell change was found on the right side, suggesting that the softening on the right side had followed the operative ablation by a few days.

Inoculations, and poliomyelitic lesions. Needle tracks of the inoculations were found in the caudate nucleus, and in the ventrolateral nuclear mass, including the pulvinar, on the left side. One inoculum was placed in the left lateral geniculate body. The most caudal inoculation had entered the left superior colliculus. There was no hemorrhage and but little softening associated with these inoculations. Typical poliomyelitic lesions, consisting predominantly of perivascular and focal mononuclear infiltrations, were present in abundance throughout most of the brain stem, especially in the subthalamus, midbrain, and hindbrain. Such lesions, however, were conspicuously infrequent in the sensory thalamus, except in regions adjoining the virus-containing inocula. Most of the perivascular and focal lesions in the left thalamus were located within the nuclei of the internal medullary lamina, in the reticular nucleus, in the nucleus centrum medianum, in the nucleus ventralis anterior, and in the nucleus medialis ventralis. These are centers which show no retrogade degeneration after cortical ablation in the monkey (Walker (12)). Within the ventrolateral nuclear group, cuffed vessels were usually seen only near the inocula. In the pulvinar, which showed more advanced retrograde degeneration than was present elsewhere, and in which several of the inoculations had penetrated, very few poliomyelitic lesions of any kind were present, even adjoining the inocula, although numerous such lesions were present in the neighboring pretectal and midbrain centers. Numerous lesions surrounded the inoculation site in the left superior colliculus.

An interesting finding was the presence of several lightly cuffed vessels and focal accumulations of mononuclear cells along the track of the inoculating needle in the left lateral geniculate body, just as

in Experiment 1. This is noteworthy because of the usual absence of poliomyelitic lesions of any sort of this center. It appears likely that the response of the mesodermal tissues in the highly resistant lateral geniculate body in this case was due to the presence in the inoculum of products of the virus-neurone reaction in the spinal cord from which the virus suspension was prepared. This would serve to explain the localization of the lesion around the needle track, and the absence of such lesions elsewhere in this nucleus.

Summary of Experiment 2. In this case virus suspension was inoculated into the left thalamus immediately after left hemi-decortication. Five days later a diagnosis of poliomyelitis was made and the animal died the following day. Retrograde neuronal change in the left thalamus was evidenced in the histological sections by a markedly pale staining reaction. Very few poliomyelitic lesions were present in the left thalamus, except in centers which showed no retrograde change, and in the immediate vicinity of the inoculations. However, numerous lesions were present in the neighboring gray centers of the pretectum and midbrain.

EXPERIMENT 3 (A-142)

Young female rhesus monkey; left hemi-decortication; inoculation of virus into left optic thalamus after three weeks

May 10, 1940. Under ether anesthesia the left cerebral hemisphere was exposed. The cortical sinus connections were closed with silver clips, the corpus callosum was sectioned, and the left hemisphere dissected away in one block. Only a small amount of blood was lost. A few hours after closure the animal was sitting up and eating a banana. She showed a typical right hemiplegia and hemianopsia with no apparent disability on the left side.

May 31, 1940. Under ether anesthesia the left side of the brain was again exposed. The dura was only loosely adherent in a few places to the underlying tissue. When the dura was reflected the general outline of the basal centers could be made out. About 0.25 c.c. of virus suspension was injected into the left thalamus with a straight needle in three sites. The early post-operative course was uneventful.

June 3, 1940. For the first time the animal showed preparalytic prodromata consisting of fever and slight head tremor.

June 4, 1940. Progressive weakness of the left arm was noted and by evening both arms including the shoulder musculature exhibited a complete flaccid paralysis. The animal otherwise showed normal aggressiveness and no other signs of

poliomyelitic paralysis. She was anesthetized with ether and perfused intravascularly with 1 per cent acetic acid in 10 per cent formol. The brain was removed and placed in the same mixture.

Histological Examination

Extent of operative ablation. Almost the entire left cerebral cortex had been removed at operation. Preserved were only the gyrus rectus, the gyrus hippocampi, and the hippocampus. Most of the head and body of the caudate nucleus, and the lateral two-thirds of the putamen had been removed or damaged, but the tail of the caudate nucleus, the amygdala, the globus pallidus, and the medial one-third of the putamen were intact. The right half of the brain was entirely normal except for a small softening, a few millimeters in diameter, at the rostral end of the gyrus cinguli.

Retrograde degeneration. The retrograde degeneration in the left thalamus was very similar in extent to that described by Walker (12) following hemidecortication, resembling especially his experiment No. 5. However, the injuries to the basal ganglia were less estensive than in Walker's case. All of the anterior nuclei, the ventro-lateral nuclear group, including the nucleus ventralis anterior and pulvinar, the nucleus medialis dorsalis, the lateral and caudal part of the parafascicular nucleus, the geniculate nuclei, the laminary nuclei, and the nucleus centrum medianum showed extremely severe retrograde degeneration. There was considerable cell loss and atrophy of the residual cells in the nucleus reticularis except at the rostral end. The cells of the nucleus centralis medialis and the nucleus medialis ventralis left of the midline were present but showed a definitely reduced staining reaction. Scattered residual cells were present in small numbers in most of the degenerated nuclei, but larger numbers of residual cells were present in the medial portion of the nucleus ventralis anterior and in the anterior end of the nucleus ventralis lateralis. The small-celled portion of the left globus pallidus showed a high degree of gliosis, but most of the neurones were intact. In the right thalamus there was retrograde degeneration only in the rostral two-thirds of the nucleus anterior medialis, corresponding to the small softening at the anterior end of the gyrus cinguli.

The retrograde degeneration in the left nucleus centrum medianum was of considerable interest because of the fact that this nucleus is

thought not to degenerate after uncomplicated hemidecortication (Walker (12)). Walker suggests that this center is connected with the globus pallidus since he observed degeneration of this nucleus in a hemidecorticate case with destruction of the globus pallidus. However, the case here presented seems to rule out this possibility since the nucleus centrum medianum was severely degenerated in the absence of any damage to the globus pallidus. Of the basal ganglia the caudate nucleus and the putamen had been severely injured, and more complete destruction of the temporal lobe was present than in Walker's case.

Inoculations and poliomyelitic lesions. The inoculation sites were uncomplicated by hemorrhage or softenings and on the left entered the ventrolateral nuclear group, the nucleus centrum medianum, the globus pallidus, and the amygdala. The rostral-most needle track extended into the right bed nucleus of the anterior commissure, and one of the more caudal inocula entered the right nucleus medialis ventralis, the right globus pallidus, and the right amygdala.

A heavy distribution of poliomyelitic lesions was present in the brain stem, especially in the pretectal region and in the midbrain. The sensory thalamus however contained very few lesions. On the left side such lesions as were present consisted of lightly cuffed vessels and small mononuclear infiltrations and were almost entirely confined to centers which showed no retrograde degeneration or to islands of residual cells in the less severely affected nuclei, such as the nucleus ventralis anterior and the anterior end of the nucleus ventralis lateralis. The pathological process had not involved the right sensory thalamus to any appreciable extent nor was the right cerebral cortex the seat of poliomyelitic lesions. The globus pallidus on both sides contained numerous lesions as did the subthalamic and tegmental centers. Perivascular cuffing and focal cellular infiltrations were numerous near the needle tracks of the inoculations except in centers which showed retrograde degeneration.

Summary of Experiment 3. Inoculation of virus suspension into the left optic thalamus three weeks after left hemi-decortication produced poliomyelitis and a distribution of lesions similar to that described in Experiment 2.

THE ABSENCE OF LESIONS IN NON-SUSCEPTIBLE NERVOUS CENTERS AFTER DIRECT VIRUS INOCULATION

It is a well-known observation that certain regions of the brain show no lesions of any kind in the course of poliomyelitis, although it is difficult to believe that these regions differ from more susceptible centers in any fundamental respect other than that the nerve cells are different in their functions and metabolism. This so-called "system selectivity" (Környey (13)) is prominent especially in the cerebral cortex. Here, for example, one area (the "motor" cortex, and especially area 4 of Brodmann) usually shows most of the pathological changes, and this response involves both neuronal and mesodermal-glial elements (fig. 6). Other regions of the cortex, however, (for example, area 17), show no response whatever, even when virus is placed directly within their substance (fig. 4), except in the immediate vicinity of the inoculum, usually no farther than 1 mm. (Bodian and Howe (11)). Hence, in regions of the cerebral cortex wherein vascular, connective tissue, and neuroglial elements must be similar to, if not identical with, those in area 4, an inoculum containing an effective dose of virus for the latter may fail to produce any pathological response, although the virus can pass from such insusceptible centers to infect other parts of the nervous system (fig. 5). Furthermore, the presence of lesions in the immediate proximity of the inoculum is proof conclusive of the capacity of the "mesodermal-glial" tissue to respond in characteristic fashion to the lesion-inducing substance in the inoculum. The occurrence of such an "area selectivity" (13) with respect to the development of mesodermal-glial lesions in the cerebral cortex is the strongest possible presumptive evidence that these lesions are secondary to the reaction of the virus with susceptible neurones, and therefore occur only in those regions in which susceptible neurones are present.

Another instance of the failure of a non-susceptible center to show lesions, even when a potent virus suspension is inoculated directly within its substance, is seen in Experiments 1 and 2, described in this report. In each of these cases one of the inoculations had entered the lateral geniculate body in which, however, lesions were found only

along the needle tracks and not in the rest of the nucleus. This finding confirms the previous presumptive evidence for the high resistance of this center to the virus, based upon the absence of lesions even when virus is inoculated into the vitreous body of the eye or into the visual area of the cerebral cortex (Bodian and Howe (11)). Furthermore, as in the case of direct inoculations into area 17, the localization of lesions only around the needle track testifies both to the capability of the mesodermal-glial tissues of these resistant centers to respond to the products of the virus-neurone reaction in the inoculum (cord suspension), and to the failure of the nerve cells of the lateral geniculate body to react to the presence of the virus itself.

DISCUSSION

It has been shown in this study, as suggested in a previous one (Bodian and Howe (11), that in a susceptible region of the brain in which most of the nerve cells, and only such cells, have been excluded by experimental means, the mesodermal-glial pathological response is greatly reduced, in the presence of the poliomyelitis virus. It is interesting in this connection to note that a similar failure of pathological response to the presence of virus occurs in the isolated olfactory bulb, ordinarily a highly susceptible center in the monkey, although the effect of the isolation (by section of the olfactory tract) is merely to alter the metabolism of the mitral cells, which show atrophy (Howe and Bodian (14)). Apparently the induced resistance of the ordinarily susceptible mitral cells is sufficient to inhibit the pathological virus response of glial and mesodermal elements as well.

Furthermore, when virus is introduced directly into a non-susceptible region of the brain (lateral geniculate body or occipital pole) mesodermal-glial lesions fail to develop, except in the vicinity of the inoculum, which itself contains products of a virus-neurone reaction (spinal cord suspension).

It appears, therefore, that the virus of poliomyelitis is not only "neurotropic," that is, possesses a predilection for nervous tissues, but is also highly neurocytotropic, or "neuronotropic," that is, it has a selective affinity for the neurone itself. Furthermore, as a result of this affinity for nerve cells (in fact, only those of certain regions of the nervous system) and from the resultant damage to the neurone,

there may arise the entire chain of inflammatory phenomena, involving mesodermal and neuroglial elements, which is characteristic of the disease entity we called "poliomyelitis." The presence of virus in the nervous tissues, by itself and in the absence of conditions necessary for reaction of the virus with susceptible nerve cells, is not synonymous with the existence of disease of the nervous tissues (as, for example, in the incubation period, however long). Only at a particular time, when the appropriate conditions of virus in relation to any susceptible nerve cells lead to the specific virus-neurone reaction, does the train of events begin which characterizes this disease of the nervous system. This chain of events may lead to "autosterilization" by a process unknown, or to reproduction of the virus within attacked nerve cells followed by spread to other neurones over axonal pathways. The response of non-neuronal elements must be considered as secondary to this virus-neurone reaction, with its obscure chain of chemical events. Possibly, also, and this point should be particularly stressed, *the reaction of virus with neurones may be responsible for chemotactic influences even before changes in the neurones are microscopically detectable*, since in some instances the response of non-neuronal elements in the nervous substance as well as in the meninges seems to precede observable changes in the nerve cells, as observed by Fairbrother and Hurst (15), Környey (13), Horanyi-Hechst (9), and others.

The fact that in many fulminating cases, neurones are killed rapidly with only a minimal mesodermal response in surrounding tissues, suggests that the chemotactic substances may be in some instances produced in greatest quantity by a slower reaction of the virus with living cells. This supposition tends to be confirmed by the frequently observed fact that in slowly developing infections, in which neuronal damage may be gradual, the mesodermal response may be very intense, and entirely out of proportion to the number of nerve cells actually destroyed (Hurst (7)). Under such circumstances it is possible that the mesodermal response may even be elicited in certain cases in places where the products of virus-neurone reaction may be quite small in amount, and the neuronal damage minimal and not detectable histologically. This probably occurs more often in the brain than in the highly susceptible spinal cord. In the brain, except in the large cells of the motor type in the brainstem and motor cortex,

the relatively high resistance of the nerve cells probably produces cell death only infrequently in comparison with the amount seen in the primary motor cells of the spinal cord.

The fact that the cellular response of the central nervous system is not elicited by poliomyelitis virus itself, appears to place the virus in a different class from pathogenic bacteria which excite cellular reaction by their mere presence in the tissues. It is thus possible for virus to attract and to be disposed of by phagocytic cells only after it has reached destructive concentrations. Whether this circumstance also exerts an indirect effect upon the humoral mechanisms which ordinarily operate to localize a noxious agent must be conjectural. The singular invasiveness of poliomyelitis virus may be favored by some such mechanism, or, on the other hand, may be dependent upon the peculiarities of axonal transmission. The factors which appear to control the progress of the virus in the central nervous system relate to its concentration and its localization in relatively constant susceptible neuronal centers and pathways. The factors determining the latter are probably chemical and, in their turn, not entirely separable from even more obscure metabolic and humoral ones which often render relatively susceptible nervous centers resistant to the effects of virus invasion either before or during the course of infection.

SUMMARY

1. When hemidecortication is performed in the rhesus monkey, most of the nerve cells in the corresponding optic thalamus which send nerve fibers to the cerebral cortex, degenerate and after several weeks disappear, leaving large regions of the thalamus devoid of nerve cells but with neuroglia, blood vessels, and perivascular tissue intact. When poliomyelitis virus is inoculated directly into such a neurone-denuded and normally susceptible region of the brain, the characteristic "mesodermal-glial" lesions of poliomyelitis, both focal and perivascular, fail to develop, although regions of the thalamus, as well as neighboring cerebral centers, which have not undergone retrograde degeneration, contain all types of lesions.

2. When virus is inoculated directly into regions of the brain such as the lateral geniculate body or occipital lobe, which appear to be normally of high resistance and contain no lesions in typical cases

of poliomyelitis, "mesodermal-glial" lesions fail to develop, except in immediate vicinity of the inoculum, which itself contains products of a virus-neurone reaction (suspension of infected spinal cord).

3. It is concluded that the mesodermal-glial response in poliomyelitis is secondary to a chemical resultant of the interaction of the virus with susceptible neurones, rather than to the direct action of the virus upon mesodermal-glial tissues. This suggests that the virus is not only "neurotropic," in the sense of Hurst (7), that is, has a predilection for nervous tissues, but is furthermore "neuronotropic" in its behavior, that is, has a selective affinity for, and probably is dependent in its growth upon living nerve cells of certain types.

4. Possible mechanisms which determine the invasiveness of poliomyelitis virus are discussed in the light of the foregoing findings.

REFERENCES

(1) Rissler, J.: Zur Kenntnis der Veränderungen des Nervensystems bei Poliomyelitis ant. acuta. *Nord. Med. Arkiv.*, 1889, **20** (Abstr. in *Fortschr. der Med.*, 1889, **7**, 500).

(2) Landsteiner, K. and Levaditi, C.: Étude expérimentale de la poliomyelite aiguë (maladie de Heine-Medin). *Ann. de l'Inst. Pasteur*, 1910, **24**, 833.

(3) Leiner, C. and v. Wiesner, R.: Experimentelle Untersuchungen über Poliomyelitis acuta. *Wien. med. Wochenschr.*, 1910, **60**, 2482.

(4) Draper, G.: *Acute Poliomyelitis*, 1917. (P. Blakiston's Son and Co., Philadelphia.)

(5) André-Thomas and Lhermitte, J.: Les lésions cérébrales et médullaires de la poliomyélite aigue de l'adulte. *Rev. Neurol.*, 1929, **51**, 1242–1250.

(6) Hurst, E. W.: The histology of experimental poliomyelitis. *J. Path. & Bact.*, 1929, **32**, 457–477.

(7) Hurst, E. Weston: The newer knowledge of virus diseases of the nervous system. A review and an interpretation. *Brain*, 1936, **59**, 1–34.

(8) Pette, H.: Über experimentelle Poliomyelitis. *Deutsche Ztsch. f. Nervenh.*, 1930, **116**, 163–169.

(9) Horanyi-Hechst, B.: Zur Histopathologie der menschlichen Poliomyelitis acuta anterior. *Deutsche Ztschr. f. Nervenh.*, 1935, **137**, 1–54.

(10) Kino, F.: Die Poliomyelitis des Hirnstammes. *Ztschr. f. d. g. Neur. u. Psych.*, 1928, **113**, 332–347.

(11) Bodian, D. and Howe, H. A.: An experimental study of the role of neurones in the dissemination of poliomyelitis virus in the nervous system. *Brain*, 1940, **63**, 135–162.

(12) Walker, A. E.: *The Primate Thalamus*, 1938. (The University of Chicago Press, Chicago.)

(13) KÖRNYEY, ST.: Die Bedeutung der mesodermalen Reaktion und der Systemelektivität in der Pathologie der Poliomyelitis. *Ztschr. f. d. g. Neur. u. Psychiat.* 1933, **146**, 724–746.

(14) HOWE, H. A. AND BODIAN, D.: An Alteration in the Susceptibility of Nerve Cells to Poliomyelitis Virus Induced by Section of their Axones. *Third Internat. Cong. for Microbiol., Proceedings*, 1939, 329–330.

(15) FAIRBROTHER, R. W. AND HURST, E. W.: The Pathogenesis of, and Propagation of the Virus in Experimental Poliomyelitis. *J. Path. & Bact.*, 1930, **33**, 17–45.

PLATE I

FIG. 1. Section through the thalamus, stained with toluidin blue (case 1). Note the severe retrograde degeneration in the ventrolateral nuclear mass and pulvinar on the left, with two deeply staining inocula placed within these centers. Focal and perivascular lesions are absent in the neurone-denuded regions containing the inocula of virus, but are numerous in the undegenerated centre median, substantia nigra, and Field of Forel on the left, and in the ventrolateral nuclear mass on the right. × 5.

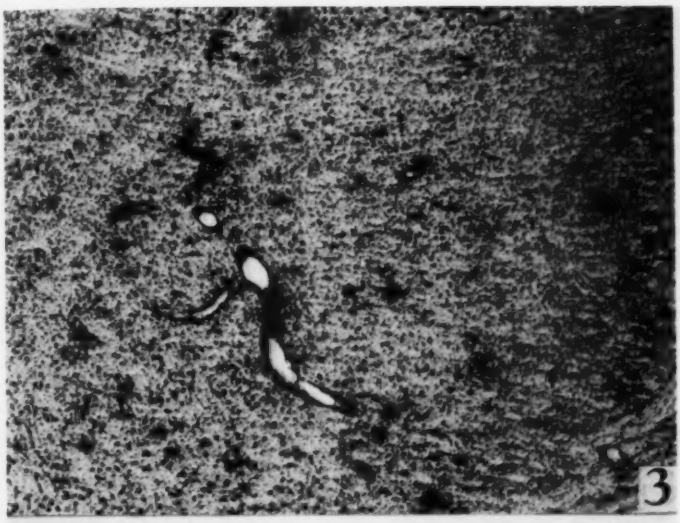
FIG. 2. Neighboring section, with higher magnification, showing two virus-containing inocula in region of retrograde degeneration (left half of section). There are no poliomyelitic lesions in this region, although lesions are present in the undegenerated centre median (right center), nucleus centralis lateralis (upper right center), and in the Field of Forel (lower right). × 12.

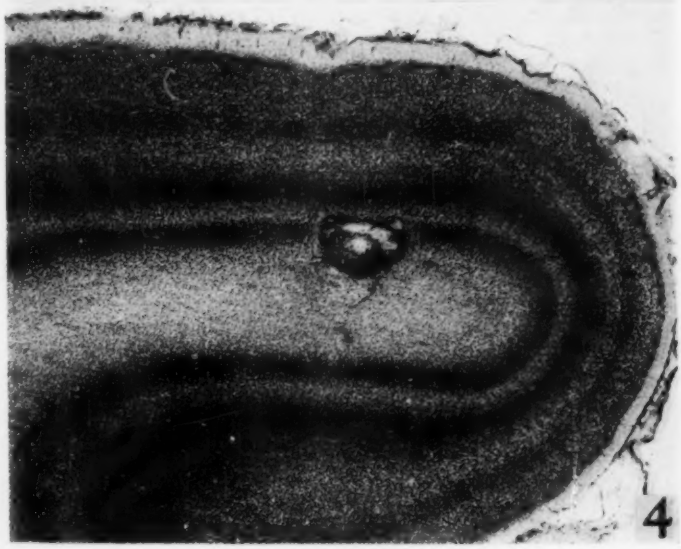
FIGS. 1–2

PLATE II

FIG. 3. Section through undegenerated right ventrolateral thalamic nuclear mass (case 1), showing by contrast the numerous focal and perivascular lesions. × 21.

FIG. 4. Section of occipital pole (area 17 of Brodmann) with potent virus-containing inoculum (center). Note the absence of response of mesodermal-glial tissues in this region of the cortex, as contrasted with the marked response in the motor cortex (area 4) shown in figure 6. × 16.



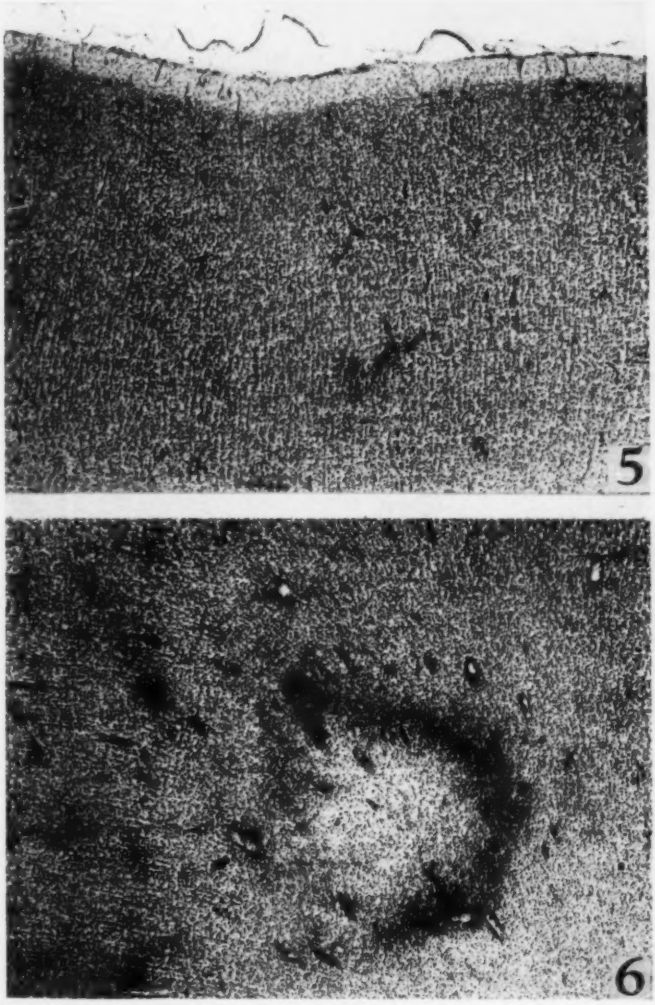


FIGS. 3–4

PLATE III

FIG. 5. Section of area 4, same case as shown in figure 4. Note typical lesions, including neuronophagia in layer of large pyramidal cells. Inoculation site in area 17. × 21.

FIG. 6. Section through motor cortex (area 4). Note the abundance of lesions, perivascular and focal, which occurs in this susceptible region of the cortex surrounding the inoculum (light area, right center) as contrasted with the absence of such lesions surrounding an inoculation site in area 17 (fig. 4). × 21.



FIGS. 5–6

A METHOD FOR THE STUDY OF NEUROMUSCULAR TRANSMISSION IN HUMAN SUBJECTS

A. M. HARVEY[1] AND R. L. MASLAND

From the Institute of Neurology and the Eldridge Reeves Johnson Research Foundation, University of Pennsylvania, Philadelphia

Submitted for publication October 28, 1940

In order to analyze the events taking place when the nerve impulse excites the muscle fiber at the motor end plate, one must have an accurate estimate both of the number of nerve fibers stimulated and of the number of muscle fibers which respond to each nerve impulse.

In animal experimental work this is done by stimulating the motor nerve with a strength of current which is sufficient to cause all of the nerve fibers to respond to each stimulus, but not strong enough to cause repetitive firing of the nerve fibers to a single stimulus. Under these conditions every nerve fiber responds once to each stimulus, and any variation in the number of muscle fibers responding must be due to failure of the nerve impulse to reach the muscle fiber. The muscle action potential may be recorded quantitatively by placing one lead in the tendon and the other in the belly of the muscle. When the temperature and the initial tension of the muscle are kept reasonably constant the resulting "belly-to-tendon action potential" is constant under normal circumstances and serves as an index of the number of fibers concerned in contraction. Any change in the total number of fibers responding causes a corresponding change in the size of the summated action potential. A change in the summated potential may also be caused by an alteration in the size of the action potential of the individual fibers.

It has been shown, however, that when such a change occurs it is accompanied by variations in the duration of the action potential as well as in its amplitude (1). For this reason, as long as the duration of the summated action potential remains constant, one may assume

[1] Present address: The Johns Hopkins Hospital, Baltimore, Md.

that variations in its size are due to variations in the number of fibers responding, and not to changes in the individual muscle fiber potentials.

Previous studies of muscle action potentials in human beings have failed to satisfy the requirements for quantitative analysis of neuromuscular transmission, for they have failed to regulate either the number of nerve fibers stimulated, or the number of muscle fibers whose response is recorded. Recently, we have been able to duplicate the conditions of animal experiments by studying the responses evoked in the muscles of the hypothenar eminence during maximal stimulation of the ulnar nerve above the elbow. The responses of normal muscles to single and repetitive stimulation at various frequencies have been studied, and the effects of certain drugs known to influence neuromuscular function have been investigated. A preliminary report of these findings has previously been presented (2).

METHODS

Experiments have been carried out with 10 normal subjects, and 20 patients suffering from various neurological abnormalities including: cerebral diplegia, tabes dorsalis, spastic paraplegia, myotonic dystrophy, multiple sclerosis, paralysis agitans, amyotrophic lateral sclerosis, primary amyloidosis, hyperthyroidism, and dystonia musculorum deformans. To some of these latter patients drugs having a curare-like action were given, and in these patients control records taken before administration of the drug showed no abnormality in neuromuscular transmission. Numerous records were obtained in each of these 30 subjects.

At the beginning of an experiment the arm was firmly fixed in a position of supination on a padded board by means of broad straps placed across the forearm, the wrist and the terminal phalanges of the fingers. An additional binding prevented adduction of the thumb. The recording electrodes consisted of small chlorided silver discs. After cleansing the skin thoroughly with ether, one electrode was firmly fixed with collodion to the skin over the ventral surface of the first phalanx of the fifth finger, and the other over the surface of the hypothenar eminence 5 cm. away. After gentle irritation of the skin and the application of a small amount of electrode jelly, the resistance between the two leads was usually found to be around 5,000 ohms. The lead over the muscle was earthed, and the electrode over the phalanx was connected to the grid input of a condenser-coupled amplifier driving a General Electric oscillograph. The time constants of the amplifier used were 100 and 1000 milliseconds. A cathode ray oscillograph was used for visual observation of the muscle action potential.

Stimulation was effected by means of condenser discharges from gas discharge

tubes which were regulated by suitable timing and trigger circuits. Stimulating electrodes consisted of a large flat metal plate placed on the forearm, and a small moveable electrode 1 cm. in diameter which could be pressed firmly over the ulnar nerve just above the elbow. Good contact was established by the use of electrode jelly, and if this was insufficient, by puncture of the skin at the site of stimulation.

Observing the action potential by means of the cathode ray oscillograph, the strength of the nerve stimulus was gradually increased until the muscle potential reached a maximum size (Figure 1, A–E). The stimulus was then increased by 10–15 per cent in order to insure supramaximal stimulation during the course of the experiment. At the end of each period of stimulation a test shock of still greater intensity was applied to make certain that the stimulating electrodes had not changed position during the period of muscle activity. Maximal muscle responses caused no undue discomfort provided the frequency of stimulation was not too great.

RESULTS

The individual action potentials obtained in these experiments were synchronous, diphasic, and constant in amplitude during the course of an experiment. Frequently the initial negative deflection had a double peak, but the shape of the potential was always constant for any given individual (Figure 1, F). When normal individuals were studied from day to day over a period of several weeks the voltage of their potentials varied by not more than 15 per cent. Although no accurate correlation could be obtained, minor changes were probably due to alterations in the skin resistance and slight changes in the position of the recording electrode. During the course of any day the change amounted to less than 5 per cent, and with a given placement of electrodes single spikes were always within 0.5 per cent of the same value. The maximum and minimum values obtained in a large series of normals ranged from 6 to 9.9 millivolts. Because of reports in the literature concerning changes in the duration of muscle action potentials in disease (3), it was felt advisable to determine the approximate normal duration according to the method we have used. Accurate determinations of total duration were difficult to make, and the figures for duration are, therefore, not as exact as are the voltage measurements. The results, however, serve the purpose of determining the normal range for the duration of this type of potential. The duration of the individual potentials was quite constant for each normal subject. The range of a series of measurements on healthy subjects was from 10.8 to 16.5 milliseconds.

Studies were made to determine the effect of the position of the electrodes on the shape and size of the recorded potential. The points

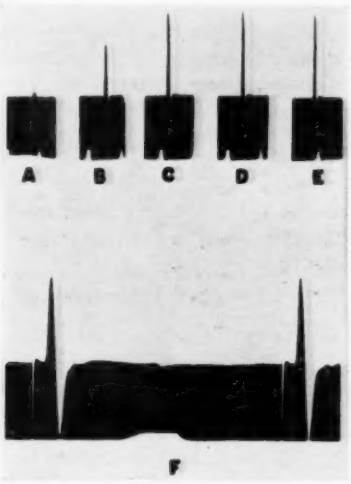


FIG. 1. A–E: normal muscle action potentials, hypothenar eminence. Strength of nerve stimulus increased by 10 per cent in successive records. The potential is maximal at C. Further increases in stimulus strength in D and E produce no further increase in the potential of the response. Time, 0.2 seconds. Potential of the maximum response, 6.8 millivolts.

F: maximal response at higher paper speed. Duration 13 milliseconds.

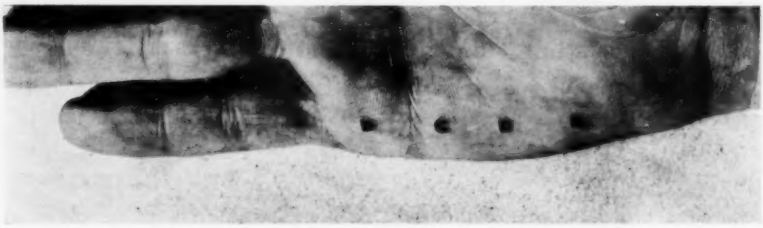


FIG. 2. Location of electrodes on the hypothenar eminence for action potential recording. The usual placement is with grounded lead at D and tendon lead at A.

chosen for study were those indicated in Figure 2. When the tendon lead remained constant and the earthed lead was moved closer to it

the potential became smaller but retained its diphasic form (Figure 3, A–C). When the earthed lead was constant in position and the tendon lead was gradually approximated to it, a similar change occurred. However, if the earthed electrode was placed nearer the origin of the muscle, the potential usually became triphasic in character with an initial positive deflection (Figure 3, E). Because of these

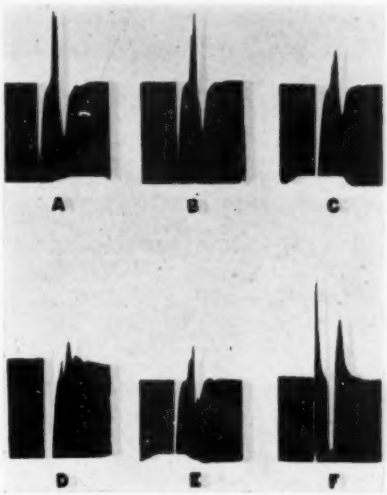


FIG. 3. Action potentials recorded from varying electrode placements as designated in Figure 2.

A. Recording electrodes at A and E.
B. Recording electrodes at A and D.
C. Recording electrodes at A and C.
D. Recording electrodes at B and D.
E. Recording electrodes at E and D.
F. Tendon lead grounded. Action potential idential with A but reversed.

findings accurate measurements of electrode position were always made in order to be able to secure comparable records from day to day in the same individual.

Even with very high amplification of the potential there was never any definite evidence of reflex activity. With the strength of stimulation employed there was probably very little sensory nerve

stimulation, for the threshold of sensory fibers is higher than that of the larger motor fibers. In addition, antidromic impulses reaching the anterior horn cells may possibly keep them in a partially refractory state.

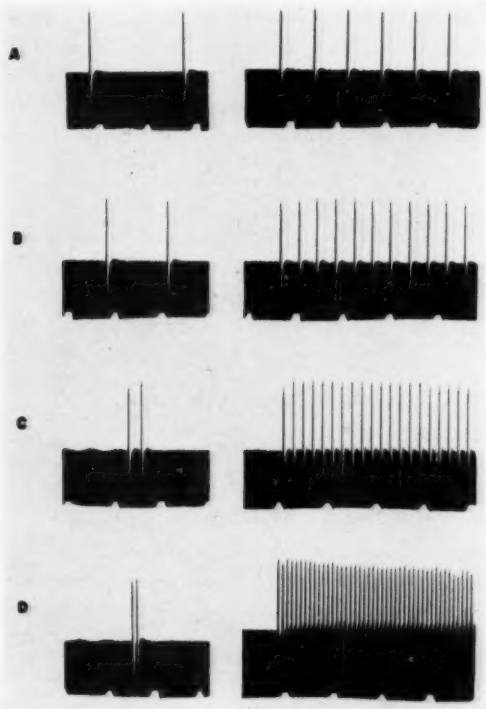


FIG. 4. Muscle action potentials. Maximal nerve stimulation at various frequencies. In the first column, responses to pairs of stimuli at varying intervals. In the second column, short periods of tetanus at various frequencies. Tiem 0.2 seconds. Potential of first response, 6.2 millivolts.

When two nerve volleys were applied from 20 to 500 milliseconds apart, the second of the two muscle action potentials was always equal to or greater than the first (Figure 4). When the interval was less than 50 milliseconds, the second response was occasionally as much as

5 per cent greater than the first. At longer intervals they were always within 2 per cent of the same size. Figure 5 shows the normal variation seen at the different intervals. The cause of the slight increase at short intervals is not known. It is not an indication of submaximal nerve stimulation. It may depend on slow potential changes following the initial response, or on some undetermined alteration in conditions existing in the region of the electrodes. The duration of the second potential was usually within 1 to 2 per cent of the duration of the first, but in many instances it was as much as 5 per cent shorter. This suggests that the second response may be more synchronized than the

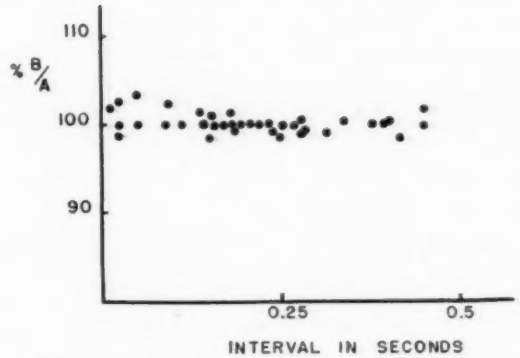


FIG. 5. Action potentials recorded from hypothenar eminence. Size of the second of two potentials of a pair (A, B) as compared to the first, plotted against interval between stimuli. Figures taken from experiments on ten normal subjects.

first, and possibly accounts for the slightly increased voltage of the second potential.

Repetitive stimulation at frequencies up to 40 per second could be continued for a period of 3 seconds with no appreciable change in the size or duration of the successive action potentials (Figure 4). At frequencies between 40 and 60 per second a gradual decline in size of from 5 to 15 per cent was noted during a similar period. At 65 to 70 per second there was a progressive decrease in voltage, reaching 45 and 35 per cent of the original value within 5 to 10 seconds. This reduction in size was accompanied by an increase in the duration of the potentials. This affected both phases of the potential equally,

and varied from 5 to 10 per cent depending on the frequency and duration of the tetanus. At slower rates of stimulation which were not accompanied by any decrease in height there was characteristically a small decrease in the duration of the positive portion of the potential. All of these changes reverted to normal very quickly. Thus, alterations resulting from stimulation at 65 per second for 15 seconds had disappeared when a test shock was applied 200 milliseconds later.

Effect of Occlusion of the Circulation: Several experiments were performed with a cuff placed on the upper arm at a pressure well above the systolic level. Over a period of 20 minutes of continuous occlusion there was no appreciable change in the voltage or the duration of the single potentials. The chief change noted was a tendency for the second of two responses at short intervals apart to be slightly greater in size than the first. The greatest difference recorded was 7 per cent at an interval of 87 milliseconds, obtained after 19 minutes of circulatory obstruction. Repetitive stimulation could not be carried out under these conditions because it resulted in intense pain.

The Effect of Quinine Methochloride: This compound which is made from quinine by the addition of a methyl group to the tertiary nitrogen group of the quinuclidine nucleus, has been shown in the experimental animal to have all of the typical actions of curarine (4). In a study of the effect of small doses of curarine on neuromuscular conduction in the cat, Brown (5) found that when two maximal motor nerve volleys are set up at varying time intervals, as the volleys become separated by a period of about 50 milliseconds there develops an increasing depression of the response to the second volley which reaches its maximum at intervals of between 200 and 400 milliseconds. At this interval the second volley may produce a response only one-half the size of the first. During a tetanus there is a progressive reduction in the size of the first ten responses, which show a steep exponential decline to 25 per cent or less of the original potential.

The applicability of the method here described to the study of neuromuscular conduction in the human, has been shown in the analysis of the effects of quinine methochloride. Following the intravenous administration of this drug in doses of 10 to 20 mgm. per kg. (15 mgm. per cc. in distilled water) given over a period of 10 to 15 minutes, effects were observed in the human which closely paralleled those observed

by Brown (5) in partially curarized animals. The degree of curarization produced by the administration of quinine methochloride could be determined by comparison of the potential of the muscle in response to a single maximal nerve stimulus before and after administration of the drug. The percentage decrease in potential furnished a satisfactory method of estimating the extent of neuromuscular block. In the human subject curarized by the injection of the quinine derivative (Figures 6 and 7), a single stimulus was followed by a long-lasting depression similar in its degree and time course to that seen in the cat. When curarization was sufficient to reduce the size of a single response by 10 to 15 per cent, a further reduction in size of the second of two

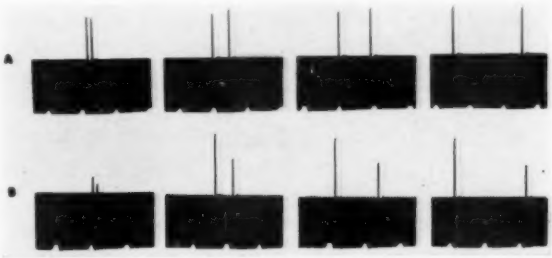


FIG. 6. A. Normal action potentials in response to pairs of stimuli at varying intervals. Time 0.2 sec. Potential of first response 6.2 millivolts.

B. Same after quinine methochloride. First pair of responses recorded at the same amplification as A. Amplification increased for subsequent pairs.

responses became evident. This reduction in the potential of the second response could be observed whenever the interval between the two stimuli was more than 15 to 25 milliseconds. Since the duration of the action potential of the muscle may be 15 milliseconds, the second response, at shorter intervals between nerve stimuli, was superimposed upon the diphasic portion of the first response and could not be measured accurately. With 40 to 50 millisecond intervals between stimuli the second potential was only 75 to 80 per cent as great as the one preceding it. Not until the interval between stimuli was almost one second did the second response begin to recover. At deep levels of curarization (50 to 60 per cent) the difference between two responses at 300 to 400 millisecond intervals was about 50 per cent. Often with

this degree of depression of neuromuscular function there has been observed a curve like that shown in Figure 7. Here it is seen that after a sharp decrease in the size of the second potential as compared to the first of a pair between 15 and 55 milliseconds apart, there is a reduction in the degree of this decrease followed again by a second drop when the interval between the two potentials is 110 to 225 milliseconds. Although we have seen this in several experiments we are unable to offer any explanation for its occurrence.

When repeated pairs of stimuli were applied with only a short interval between each succeeding pair, the second response of each pair

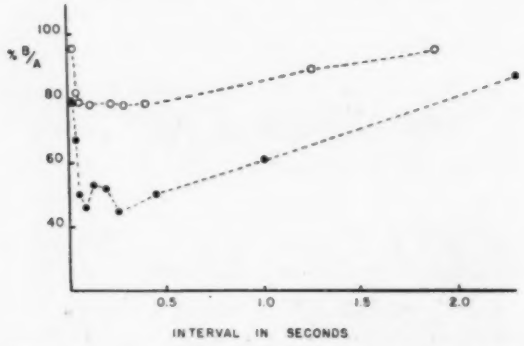


FIG. 7. Size of second of two potentials of a pair (A, B) as per cent of the first, plotted against interval between stimuli. Shows time course of the depression at two levels of curarization. Circles show mild, solid dots marked curare effect.

remained constant in size, but the first rapidly diminished until the two spikes of each pair became equal in size. This served to emphasize the duration of the depression which follows stimulation and showed the importance of allowing adequate rest between test stimuli.

As one would expect, the duration as well as the size of the second potential was decreased. Thus, there is no possibility that the depression observed is the result of increased temporal dispersion, and one must conclude that it is due entirely to a reduction in the number of muscle fibers contracting.

When the nerve was stimulated repetitively at a rate of 10 to 15 per

second the successive spike heights showed a progressive decline to less than 50 per cent of their original value, and remained fairly constant at this level (Figure 8). If one then administered a test shock at increasing intervals after the tetanus, a gradual increase in the size of the response was observed until the original amplitude was reached at periods 1.5 to 2.0 seconds after the termination of the tetanus. The

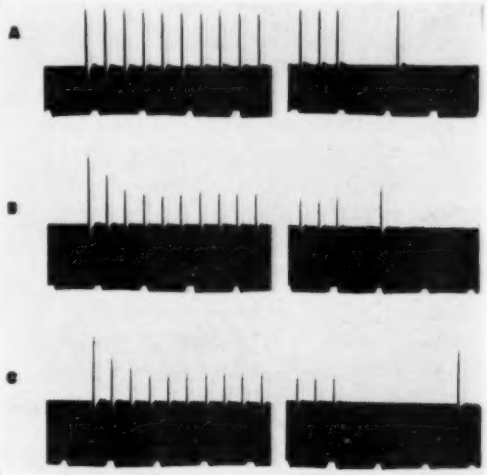


FIG. 8. Muscle action potentials in response to repetitive stimulation of motor nerve for three seconds. A section of each record has been cut out between the first ten and the last three responses. The last potential in each record, in the right hand column, is the response to a test stimulus. A, control. B and C, after quinine methochloride. Note the length of the depression which follows the tetanus, as indicated by diminution of the size of the potential responses to the test shock which follows. Potential of the first response in A, 6.1 millivolts, in B and C, 4.8 millivolts. Time 0.2 sec.

accuracy with which these findings could be recorded in the human subject was comparable to that attained in the experimental animal where the potentials were recorded from the exposed surface of the muscle. The findings in the human subject were both qualitatively and quantitatively similar to those obtained in animal experiments; a fact which is convincing evidence of the value of this type of recording for the study of human muscle physiology.

DISCUSSION

The changes in the normal action potential as a result of repeated stimulation are of interest. The first alteration is always in the second phase of the potential. There is a decrease in amplitude accompanied by an increase in duration. This is indicative of temporal dispersion in the fiber response, but it is not of sufficient degree to account wholly for the reduction in voltage. There must be, in addition, fewer muscle or nerve fibers responding. In contrast to this more complicated change in shape and amplitude are the alterations following partial neuromuscular block by quinine methochloride. Here the voltage is decreased as is also the duration. These are the changes which would be expected when a reduced number of muscle fibers were responding to each nerve impulse. Brown has suggested (5) that these phenomena are best explained by the diminished output of acetylcholine with successive stimuli, which becomes apparent only when a curarizing agent has raised the threshold of the muscle fibers to this substance.

In many experiments after the administration of quinine methochloride the potentials evoked by a train of stimuli show, after the initial rapid decline in amplitude, a gradual return to a slightly higher level. This level, which is much lower than that originally recorded, is maintained at low levels of stimulation (20 to 25 per second), but when the rate is higher a second gradual decline in voltage may take place. Although there is no way of making an accurate correlation, it is possible that this secondary rise may be associated with a mobilization of potassium ions during muscle activity. It is known that potassium is a decurarizing substance and the decurarizing ability of a tetanus is thought to be due to the mobilization of the potassium ions (6).

The method here described should find several spheres of usefulness. Experiments are being carried out in patients suffering from myasthenia gravis, muscular dystrophy, and family periodic paralysis to see if there are changes from the normal which may aid in elucidating the mechanism of the abnormal function in these diseases. If changes are found, the quantitative nature of this technique should be useful in following the course of the disease and judging the value of therapeutic agents. Because of the quantitative relation of the voltage of the muscle action potential to the actual number of muscle fibers

responding, the method can also be used as an index of the number of motor nerve fibers stimulated. Studies of changes in nerve excitability and threshold can thus be made. A maximal stimulus can be administered and then followed by submaximal volleys at different time intervals. The size of the muscle potential evoked by these test shocks should furnish an index of changes in excitability of the nerve.

SUMMARY

1. A method has been described for recording quantitatively the muscle action potential from the hypothenar eminence of human subjects in response to maximal stimulation of the motor nerve.

2. The normal values for voltage and duration of these potentials following various frequencies of nerve stimulation have been determined.

3. The changes produced by circulatory obstruction and those indicative of fatigue following stimuli of high frequency have been recorded.

4. Studies have been made in subjects partially curarized by means of quinine methochloride. It has been demonstrated that the results obtained in such subjects are qualitatively and quantitatively comparable to those recorded under similar conditions in the experimental animal.

5. The value of this method for studying the abnormal mechanisms concerned in muscle diseases, and for following the course of these diseases under treatment, has been discussed.

REFERENCES

(1) HARVEY, A. M.: *J. Physiol.*, **95:** 45, 1939.
(2) HARVEY, A. M., R. L. MASLAND AND R. S. WIGTON: *Am. J. Med. Sc.*, **199:** 878, 1940.
(3) EICHLER, W., P. HOFFMAN AND H. RUFFIN: *Deutsch. Zeitschrift f. Nervenheilkunde*, **137:** 147, 1935.
(4) HARVEY, A. M.: *Bull. Johns Hopkins Hosp.*, **66:** 52, 1940.
(5) BROWN, G. L.: *J. Physiol.*, **92:** 23 p., 1938.
(6) BROWN, G. L. AND U. S. VON EULER: *J. Physiol.*, **93:** 39, 1938.

SULFANILYLGUANIDINE IN THE TREATMENT OF ACUTE BACILLARY DYSENTERY IN CHILDREN[1]

E. K. MARSHALL, JR., A. CALVIN BRATTON,[2] LYDIA B. EDWARDS[3] AND ETHEL WALKER

Department of Pharmacology and Experimental Therapeutics, Department of Preventive Medicine, and Department of Pediatrics, The Johns Hopkins University

Submitted for publication November 13, 1940

In a recent publication, the results of an experimental study of sulfanilylguanidine have been presented (1). The properties of this drug suggest that it or some other compound having similar properties may prove useful in the treatment of bacterial infections which are mainly or entirely localized in the intestine. The present communication presents a preliminary report of the trial of the drug in acute bacillary dysentery. Data are also presented to show that saturation of the intestinal contents with the drug can be obtained with a dosage which gives a low concentration in the blood, thus confirming deductions made from experimental observations on animals.

The drug used in the present investigation was prepared by one of us (A. C. B.) by the method previously described (1). The monohydrate was used throughout; all dosages are expressed in terms of this, while all figures for blood and stool concentrations are given in terms of the anhydrous compound.[4]

BLOOD AND STOOL CONCENTRATION OF SULFANILYLGUANIDINE

The method used for determining sulfanilylguanidine in stools was as follows. The total stool was thoroughly mixed, and a five- to ten-

[1] This investigation has been aided by a grant from The John and Mary R. Markle Foundation.

[2] Lalor Foundation Fellow.

[3] E. R. Squibb and Son Fellow in Preventive Medicine.

[4] After completion of our studies on children and a few adults with our own preparations of sulfanilylguanidine, we obtained a supply of this drug from the Calco Chemical Company, which was used in our subsequent studies in most of the adults upon whom blood concentrations are reported. We wish to thank the Calco Chemical Company for furnishing a supply of this drug.

gram sample weighed out. About 150 cc. of warm water were added and the mixture was emulsified by mechanical stirring. Twelve cc. of a 50 per cent solution of trichloroacetic acid were added, followed by further emulsification. The mixture was diluted to 200 cc., and a portion filtered. After appropriate dilution of the filtrate, a determination of sulfanilylguanidine was made as previously described (1). Recovery of sulfanilylguanidine added to normal stools was quantitative.

Blood concentrations were determined[5] in children on 0.04 cc. samples of blood, precipitated in a 1:200 dilution, in adults on 0.5 cc. samples with a 1:50 dilution, by the method already described (1).

In table 1 are presented data on the concentrations of sulfanilylguanidine present in stools and blood obtained from patients receiving the drug by mouth. The first six patients were children with intestinal bacterial infections. The last patient was an adult with an ileostomy, from whom samples of excreta were obtained before passage through the large intestine. Regardless of the particular dosage schedule used, all blood samples were taken four hours after a dose of drug as the most probable time to obtain the peak concentration. One cannot be certain that this object was always obtained. However, for the purpose of this investigation, the general level of the blood concentrations from day to day was considered of more importance than data on the blood concentration-time curve.

Sulfanilylguanidine has been found to be soluble in water at body temperature to the extent of about 200 mgm. per cent (1). A survey of the figures given in table 1 indicates that the concentration of the drug in the stools, obtained under various dosage schedules, is usually sufficient to give a saturated aqueous solution. This was anticipated from the studies of the pharmacological properties of the compound. The data given in case 7 show that material leaving the end of the small intestine, in most instances, contains the drug in concentrations greater than 200 mgm. per cent. In cases 1 and 2, administration of a maintenance dose of 0.1 gm. per kgm. every 12 hours appears to result in stool concentrations above the saturation

[5] Sulfanilylguanidine can be determined in blood and urine by the method used for sulfanilamide and its derivatives (2). Precipitation of proteins in a 1:20 dilution gives quantitative recovery of both free and conjugated drug.

TABLE 1

Concentration of sulfanilylguanidine in stools and blood

	DATE	BLOOD CONCENTRATION (MGM. PER CENT)		CONCENTRATION IN STOOLS (MGM. PER CENT)	NO. OF STOOLS PER DAY
		Free	Total		
1. Bacillary dysentery. 6/8 Initial dose, 0.2 gm./kgm. Maintenance dose, 0.1 gm./kgm. q.12.h.	6/21			380, 400, 980	3
	6/22			961, 702, 340	5
	6/23			585	1
	6/24			220	1
2. Bacillary dysentery. 6/18 Initial dose, 0.2 gm./kgm. Maintenance dose, 0.1 gm./kgm. q.12.h.	6/24			694	3
	6/25			289, 658	4
3. Typhoid fever. 8/13 Initial dose, 0.1 gm./kgm. Maintenance dose, 0.05 gm./kgm. q.4.h.	8/17	1.0	1.2	3030	4
	8/19	1.7	1.8	2900	2
	8/20	1.4	2.0	1810	2
	8/21			1230	2
	8/22	2.1	3.0	1730, 2000, 2190	3
	8/24			1130	1
	8/26	3.8	3.5	1620, 1740	2
	8/28	3.6	3.3	2010, 1550	2
	8/30	2.1	1.9	962, 1130	2
4. Bacillary dysentery. 7/20 Initial dose, 0.2 gm./kgm. Maintenance dose, 0.05 gm./kgm. q.4.h. until 7/22, then 0.1 gm./kgm. q.8.h. until 7/27	7/22	4.0	4.3	4300, 3200	2
	7/23	0.8	1.1	1390	2
	7/26	3.0	3.7	964	1
	7/27	1.3	1.8	403, 388	2

5. Infection with S. enteritidis. 7/25 Initial dose, 0.2 gm./kgm. Maintenance dose, 0.05 gm./kgm. q.4.h. until 7/31, then 0.1 gm./kgm. q.8.h. Drug discontinued 8/3	7/25			393, 1265, 1405	8
	7/26	2.5	3.0	3400, 298, 328, 1450, 1015, 201	6
	7/27	1.3	1.8	165, 132, 260, 76	5
	7/28	3.2	—	1415, 1962, 723, 260, 2010, 2575	7
	7/29	3.0	4.2	1750, 883, 654, 317, 1065	5
	7/30	1.8	2.5	525, 365	3
	7/31	3.1	3.8	508, 308, 1090	3
	8/1	3.4	3.9		5
	8/2	2.9	4.0	5190, 2450	4
6. Bacillary dysentery. 8/6 Initial dose, 0.2 gm./kgm. Maintenance dose, 0.05 gm./kgm. q.4.h. until 8/12, then 0.1 gm./kgm. q.8.h.	8/6			491, 7700, 24100, 26900, 4750	16
	8/7	2.6	4.9	1060, 150, 165, 273, 877, 1060, 226, 344	10
	8/8	2.2	2.3	161, 1100, 1375, 1061, 595, 1040	7
	8/9	1.9	2.2	118, 72, 127, 294, 362, 244, 495	11
	8/10	2.6	2.9	530, 231, 554, 667, 628, 559, 326	8
	8/11	1.8	2.4	179, 188, 218, 192	5
	8/12	1.9	2.3	362, 336, 418, 454, 415, 334	7
	8/13	2.4	2.4	144, 165, 198, 357, 570	5
	8/14	1.1	1.1	311, 1187, 64	3
	8/15	1.2	1.5	1460, 435, 469, 539, 195, 224, 2960	5
	8/16	1.4	1.5	524, 899	4
7. Ulcerative colitis. 8/12 Initial dose, 0.1 gm./kgm. Maintenance dose, 0.1 gm./kgm. q.8.h. until 8/16. After 8/16 maintenance dose, 0.05 gm./kgm. q.4.h. Drug discontinued 8/20. Ileostomy discharge collected for analysis	8/12	2.4	3.0	354, 241, 222, 125, 46, 145	6
	8/13	4.7	6.5	397, 562, 2950, 524, 776, 179, 58	
	8/14	4.6	6.6	315, 706, 11750, 283, 6, 278, 667, 93, 168	9
	8/15	4.8	7.0	866, 748, 119, 558, 270, 144, 25, 441	8
	8/16	4.1	6.2	486, 318, 2080, 55, 183, 322, 174, 144	8
	8/17	4.6	6.5	634, 1090, 2670, 360, 365, 298, 280, 200	8
	8/18	5.5	7.5	397, 1440, 1700, 1990, 256, 207, 132, 250, 55, 215	10
	8/19	5.6	7.5	262, 965, 170, 246, 370, 387, 312	7
	8/20	5.7	7.5	276, 747, 3690, 390, 58, 12, 11	7

level for an aqueous solution. However, the number of stools here was only 1 to 5 per day. In case 3, with a maintenance dose of 0.05 gm. per kgm. every 4 hours, much more than sufficient drug was present to insure saturation with a rate of evacuation of 1 to 4 per day, while the blood concentration of drug remained at a low level. In case 4, a maintenance dose of 0.1 gm. per kgm. every 8 hours gave stool concentrations above 200 mgm. per cent, with blood concentrations similar to those found in case 3. In case 5, when the number of stools per day varied from 5 to 8, a maintenance dose of 0.05 gm. per kgm. every 4 hours gave stools which in 4 instances out of 26 contained less than 200 mgm. per cent of the drug. In case 6, a maintenance dose of 0.05 gm. per kgm. every 4 hours, with 5 to 16 stools per day, gave 24 per cent of stools with concentrations below 200 mgm. per cent; while a maintenance dose of 0.1 gm. per kgm. every 8 hours, with 3 to 7 stools per day, resulted in 22 per cent of stools with concentrations below 200 mgm. per cent. There was, however, only one instance with either dosage schedule where the stool concentration of drug fell below 100 mgm. per cent. In case 7, 30 stool analyses showed 11 with concentrations below 200 mgm. per cent and 5 below 100 mgm. per cent when the maintenance dose was 0.1 gm. per kgm. every 8 hours; 33 analyses showed 7 with concentrations below 200 mgm. per cent and only 2 below 100 mgm. per cent when the dosage was 0.05 gm. per kgm. every 4 hours.

Certain data are available on the concentration of sulfanilylguanidine in the blood with various dosage schedules. In children, with a maintenance dose of 0.05 gm. per kgm. every 4 hours, 54 determinations on 17 patients gave an average value for free 1.91 and total 2.52 mgm. per cent; with a maintenance dose of 0.10 gm. per kgm. every 8 hours, 30 observations on 11 patients showed an average of free 2.26 and total 2.81. In the first group, the average acetylation was 24.2 and in the second 19.6 per cent of the total. In adults, 27 observations on 5 patients with a maintenance dose of 0.05 gm. per kgm. every 12 hours gave an average of free 2.59 and of total 3.43 mgm. per cent; 60 observations on 13 patients with the same dosage every 8 hours showed free 2.12 and total 3.16; 13 observations on 4 patients with this same dose given every 4 hours gave an average value of free 3.29 and total 4.41 mgm. per cent. In the three groups the

average per cent acetylation of the total concentration of drug was 24.5, 32.8, and 25.4, respectively. Tables 2 and 3 show the distribution of the values and of the per cent of the total which is acetylated in the blood, excluding the small number of observations on the 4-hour dosage schedule in adults. It is to be noted that blood concentrations are higher in adults than in children with the same dosage schedule and that there appears to be a slightly greater acetylation in adults than in children.

TABLE 2

Blood concentrations of sulfanilylguanidine four hours after a dose

	MGM. PER CENT							
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
Children								
No. of observations, free drug	10	38	26	7	2	0	1	0
No. of observations, total drug	3	29	27	17	5	2	0	1
Adults								
No. of observations, free drug	4	37	36	4	5	0	1	0
No. of observations, total drug	0	9	36	28	8	1	5	0

TABLE 3

Percentage of sulfanilylguanidine in acetylated form in blood

	PER CENT ACETYLATED					
	0-10	10-20	20-30	30-40	40-50	50-60
Children, no. of observations	30	36	35	13	3	1
Adults, no. of observations	3	13	18	42	11	0

Twenty-four hour total urine collections were made in cases 5 and 7 (table 1). In case 5, with a dosage of 0.05 gm. per kgm. every 4 hours, the average urinary excretion of drug was 13 per cent of the amount ingested per day. The per cent acetylated averaged 31. In case 7, the average excretion was 21 per cent on the 8-hour dosage, with 36 per cent acetylation, and 25 per cent with 33 per cent acetylation on the 4-hour schedule, the total daily dosage being the same in each case.

CLINICAL RESULTS

Clinical experience with the sulfanilylguanidine treatment of acute bacillary dysentery in children includes 17 cases where the diagnosis was substantiated by the recovery of the dysentery organism from the stools. All the children were patients on the wards of the Harriet Lane Home.

The summer and fall of 1940 saw so few cases of intestinal diseases in children in Baltimore that any attempt to run a controlled experiment as to the efficacy of the drug was impossible. Therefore, all definitely ill children thought on admission to have acute bacillary dysentery were treated with sulfanilylguanidine. When the diagnosis was doubtful as to whether the patients suffered from bacillary dysentery or non-specific diarrhea, the drug was administered while awaiting the results of stool cultures. And finally several children were likewise treated although the admission diagnosis was a non-specific diarrhea; in some of these the dysentery bacillus was isolated. All cases in which the dysentery organism was not cultivated from the stools have been excluded from the tabulated results (table 4).

Treatment with the drug was usually begun within 24 hours of admission or as soon as the diagnosis of probable dysentery was made. In a few cases treatment was withheld or given later in the illness in order to evaluate the effectiveness of other therapeutic measures, including adequate fluids, proper feeding, and good nursing in general. Various schedules for drug administration were used. Initial doses were either 0.1 or 0.2 gm. per kgm. while maintenance doses varied from 0.1 gm. every 8 or 12 hours to 0.05 gm. per kgm. every 4 hours.

Other aspects of the management of the patients were those standard for gastro-intestinal disorders on the Harriet Lane Home wards. In clear-cut cases of dysentery, feedings were given as tolerated from the time of admission on. In the presence of vomiting, distention, or severe dehydration, a preliminary period of starvation was used. In the instances where the diagnosis on admission was of a non-specific diarrhea, the patients were similarly starved. Parenteral fluids were administered as required, using the subcutaneous or intravenous route. Continuous intravenous drips were used for the severely dehydrated children. Transfusions were given in the few cases where anemia or hypoproteinemia was present.

In addition to the usual examinations performed on every ward patient, these children had frequent stool cultures from freshly passed stools during the first few days and thereafter once daily when possible, blood cultures on admission (all of which were sterile), and hemoglobin and leukocyte determinations repeated every two days during the period of sulfanilylguanidine administration.

TABLE 4

Sulfanilylguanidine therapy in acute bacillary dysentery in children

HISTORY NO.	AGE	STOOL CULTURE	DAY OF DISEASE TREATMENT BEGUN	TIME OF ADMINISTRATION OF DRUG	STATUS BEFORE ADMINISTRATION OF DRUG		STATUS AFTER ADMINISTRATION OF DRUG DAYS IN WHICH:		
					Temperature maximum	No. of stools	Temperature normal	Condition markedly improved	Diarrhea checked
				days					
A-9337	23 mos.	Flexner	1	5	39.5	20+	1	1	1
A-4654	3 yrs.	Sonné	1	6	40.6	7	1	1	1*
A-11152	20 mos.	Sonné	1	4	39.5	5	1	1	1
85734	1 yr.	Sonné	2	7	39.5	8	2	2	3
A-16296	5 yrs.	Flexner	2	12†	41.4	18	1	1	6
A-16293	18 mos.	Flexner	3	10†	39.8	15	1	1	8
A-16689	2 yrs.	Flexner	3	6	40.1	6	1	1	1
A-11197	2 yrs.	Flexner	4	13	40.8	15	5	1	12
A-17210	10 mos.	Flexner	6	6	39.0	12	1	1	2
A-6340	3 yrs.	Flexner	7	5	39.0	12	2	2	3
A-6830	2 yrs.	Flexner	7	7	38.4	13	1	Slow improvement	8
A-15141	6 mos.	Flexner	8	19	41.4	6	7	Slow improvement	10
A-16338	8 mos.	Sonné	9	12	38.2	11	2	Slow improvement	10
A-14616	11 mos.	Flexner	10	11	39.5	16	5	Slow improvement	10
99513	4 yrs.	Flexner	10	6	38.6	6	1	Slow improvement	4
A-14242	13 mos.	Flexner	12	3	38.0	7	1	No change	2
A-17555	8 mos.	Flexner	16?	14	40.0	20	5	Slow improvement	21

* Occasional abnormal stool later.

† Twelve hour interval between doses of drug.

The accompanying table 4 presents the results in the 17 cases of acute bacillary dysentery treated with sulfanilylguanidine. Some explanations are needed. All cases were started with the drug on a 4-hour schedule except the two cases marked with a double asterisk where it was given at 12-hour intervals. "Status before Administration of Drug" refers to the 24-hour period before chemotherapy was begun. Where treatment was started immediately after admission, the maximum temperature refers to the highest temperature recorded during the first 24 hours in the hospital. Under "Status after Admin-

istration of Drug" the figures given are in terms of days of therapy, not in terms of days of disease. All temperatures were taken rectally. The temperature was considered normal when it remained constantly below 38°C. (100.4°F.). In the description of the effect of the drug on the stools, neither the number nor the characteristics of the stools furnished a satisfactory measure of improvement. In this table, therefore, we have arbitrarily defined the diarrhea as checked when the stools were 4 or less in number daily, were formed, and were without gross pus or blood. In most patients the transition to normal or constipated stools was fairly rapid, but occasionally the stools continued softer than normal or showed a little mucus after the time noted as marking the subsidence of the diarrhea.

Consideration of these cases according to the period of the disease in which chemotherapy was begun shows at once that the results of treatment instituted early in the disease differed rather strikingly from the results of treatment later in the illness. In the 7 children treated on or before the third day of disease, the results were uniformly good. All were young children, under 5 years of age; all had high fever prior to chemotherapy; 4 had had convulsions; and 6 of the 7 were seriously ill. Within 28 hours, and frequently much sooner, after sulfanilylguanidine was begun, the temperature had fallen to below 38°C. (100.4°F.) in every case and the children remained afebrile during the rest of their stay on the ward. Within 12 to 36 hours after the drug was started there was a marked improvement in the general condition, some of the children appearing almost well after only 24 hours of chemotherapy. The diarrhea was checked in from 1 to 3 days in all children given sulfanilylguanidine on a 4-hour schedule. In this group of early treated cases, the two children who received the drug on a 12-hour schedule did not establish normal stools until the 6th and 8th day, respectively, of sulfanilylguanidine therapy although the temperature fell and the general condition improved markedly within 24 hours after the treatment was begun.

Ten children were treated late in the disease, the institution of chemotherapy varying from the 4th to the 14th day of the disease. In this group the results were not uniform. Some cases showed the same striking improvement that occurred in the children treated

early, but the majority ran a course uninfluenced by the administration of sulfanilylguanidine.

In 10 of this group of 17 children, the stool cultures became negative for dysentery organisms during treatment and remained negative during hospitalization. In five other cases the stools became negative on the last day of therapy or within two days after its discontinuance. One child had an inconstant positive culture (Sonné) during and after drug administration. The remaining child had a negative culture before starting chemotherapy. Because of lack of definite evidence that the sulfanilylguanidine in the stools does not in some cases prevent the growth of the dysentery organism, only negative cultures obtained after cessation of chemotherapy can be considered significant.

In addition to these 17 cases of proven acute bacillary dysentery, three infants were treated with sulfanilylguanidine who were thought to have the disease but whose stools failed to yield a dysentery organism on culture. One 14-month old baby was treated on the first day of a clinically typical attack of acute dysentery and had the same dramatic cure in 24 hours as was noted in the group receiving early treatment, but no pathogenic organism could be isolated from the stools although they contained blood and pus. On the 11th day of illness this child's serum had no agglutinins against any of the dysentery group of organisms. Two other infants, aged 5 and 8 months, respectively, were treated on the 3rd and 4th day of an acute gastro-enteritis, without beneficial effect. A variety of Salmonella enteriditis was cultured from the stools of one of these children and the Morgan bacillus, and later a variety of Salmonella enteriditis, from the stools of the other.

Several children suffering from other forms of gastro-intestinal disease were also treated with the drug. Two babies with chronic bacillary dysentery, one 13-year old girl with typhoid fever, and one 13-year old boy with chronic ulcerative colitis were given the drug without evidence of any alteration of the natural course of the disease. The number of these cases, however, is too small to allow any conclusions as to the possible effectiveness of the drug in these conditions.

Dr. George M. Lyon of Huntington, West Virginia, has treated a number of cases of bacillary dysentery with sulfanilylguanidine. Dr.

Lyon has kindly allowed us to quote the following brief summary of his results.

"Twenty cases of severe acute bacillary dysentery were treated with sulfanilylguanidine and twenty cases of a similar severity and clinical picture were taken as untreated controls. Alternate cases were treated.

"In order to have the cases of as similar a clinical character and severity as possible, certain criteria were established as a prerequisite for selection. The patients must have had an elevation of temperature of 102°, and either a stool culture positive for dysentery bacillus or have had diarrheal stools containing pus or blood and pus. They must have been seen in the first week of illness.

"The clinical course of the untreated cases was that with which we are so familiar: temperatures of 102–105° for the first week with severe bloody diarrhea, abdominal cramps, vomiting, and prolapsus ani; and in the second week a lower temperature, a continuation of the diarrhea which becomes more purulent than bloody and a loss of strength and body weight; in the third week, a tendency to enter a convalescence of varying degrees of severity and tardiness, indigestion and loss of strength being the important features.

"Of the treated cases, five seemed to follow the general course of the untreated cases. One case showed a good therapeutic response, and fourteen showed an excellent therapeutic response. Many recoveries were, indeed, most dramatic in character. These cases generally showed a rather rapid fall in temperature and leukocyte count within 48 to 72 hours, a closely paralleling general clinical improvement, a marked reduction in number of diarrheal stools, and improvement in the character of the stool in the first 48 to 72 hours after institution of the chemotherapy."

Toxic Effects. No definite toxic effects have been observed in our series of 25 children who have been given therapeutic doses of sulfanilylguanidine. Occasionally vomiting was present for a short period after chemotherapy was begun, but this occurred in sick children who vomited prior to the administration of the drug. As soon as the general condition improved, the vomiting ceased, although the drug was continued. Three children showed during therapy a fall in hemoglobin of moderate degree, not attributable to the correction of dehydration. As this occurred during the active phase of the disease, it was felt it could not be definitely attributed to the sulfanilylguanidine administration. No hematuria was seen. In one case bright red urine was passed on two occasions, but the urine contained no blood by chemical test and it cleared spontaneously. No effect of sulfanilylguanidine was apparent on the leucocyte count. This count varied between 2,500 and 30,800 and during chemotherapy

it tended to return to normal. None of the children developed rashes or had drug fever. It must be stressed, however, that with one exception none of these children received the drug for more than fourteen days, the fluid intake was always adequate, and a careful watch was kept for any evidence of renal insufficiency.

In 25 adults receiving the drug for a variety of conditions, toxic reactions occurred or were suspected in three. One patient (J.H.H. 210246) developed drug fever and unilateral conjunctivitis on the second day of drug therapy. In another (J.H.H. 106738) a possible mild hemolytic anemia occurred on the third day of sulfanilylguanidine administration. In a third (J.H.H. 148937) fever occurred on the eighth day of sulfanilylguanidine administration.

Dosage. In view of the data presented above on stool and blood concentrations of this drug and the clinical response with varying dosage schedules, the following dosage program is recommended for the further trial of sulfanilylguanidine in acute bacillary dysentery in children: Initial dose *per os* 0.10 gram per kilogram, maintenance dose 0.05 gram per kilogram every four hours until the number of stools per day is four or less, then 0.10 gram per kilogram every eight hours for at least three days.[6] The finely powdered drug is administered in milk or in water suspension. We have no definite information at present concerning the most suitable length of treatment to prevent relapse after the signs of the disease have abated. Our impression at present is that the drug should not be continued longer than fourteen days because it is doubtful if longer treatment will be beneficial. Furthermore, such limitation of treatment minimizes the possibility of agranulocytosis, which with other sulfonamide drugs does not occur before the fourteenth day (3).

SUMMARY

Sulfanilylguanidine can be given to patients (both children and adults) in dosage sufficient to insure saturation of the intestinal contents with the drug, but to give a very low concentration of drug

[6] In adults the dosage schedule used in bacillary dysentery has been the same as for children except that when the drug is given every 8 hours 0.05 gram per kilogram is given instead of 0.10 gram per kilogram. The drug has been used in adults in other conditions than bacillary dysentery in a dosage of 0.05 gram per kilogram every 8 hours.

in the blood. The results of the treatment of bacillary dysentery in a small group of children are reported. These results appear to be sufficiently encouraging to warrant further clinical trial of the drug.

APPENDIX—SUMMARY OF CASES

1. Treatment begun within three days after onset of disease

A-9337, male, colored, aged 23 months. Admitted on first day of illness. Chief symptoms: high fever, a convulsion, severe diarrhea. In the short period before admission he had passed 20 or more stools, containing blood, pus and mucus. He was seriously ill but not dehydrated at the time of admission. His temperature was 39.5°C. (103°F.), and the white blood cell count was 8600. The Flexner type of dysentery organism was isolated from the stools passed during the first 48 hours in the hospital. As soon as cultures had been obtained, the baby was started on sulfanilylguanidine. His temperature dropped to normal within 12 hours. On the second day of therapy the child seemed almost well and had no stools at all. On the following day he passed 3 stools, all formed, and thereafter all his stools were normal. Sulfanilylguanidine was discontinued after 5 days and the child was discharged in good condition on the 10th day.

A-4654, male, colored, aged 3 years. Admitted on first day of illness. Chief symptoms: high fever, a convulsion, diarrhea. In the 12 hours before admission he had passed 7 stools. On entry he was seriously ill, with a temperature of 40.6°C. (105°F.), and a leucocyte count of 6000. His frequent loose stools contained blood, pus and mucus, and on culture yielded the Sonné type of dysentery organism. He was treated with sedatives and parenteral fluids, and later in the day sulfanilylguanidine was begun. His temperature was normal within 4 hours and his general condition markedly improved within 12 hours. During the first day of chemotherapy he continued to have frequent loose stools, but the gross blood rapidly disappeared, and the following day there were only three stools all of which were formed. On the third day in the hospital the child appeared practically well. Stools continued to be pasty during the remainder of his stay in the hospital, but on two occasions contained a little blood or mucus; twice, although of normal character, the stools numbered five daily. Sulfanilylguanidine was discontinued after the 6th day, and the child was sent home on the 14th day.

A-11152, male, colored, aged 20 months. Admitted on first day of illness. Chief symptoms: fever, diarrhea. He had passed 4–5 loose stools showing blood, pus and mucus during the 6 hours of illness. On admission he was only mildly ill, although his temperature was 39.5°C. (103°F.). The leucocytes numbered 7200. The Sonné type of dysentery organism was isolated from the stools. Sulfanilylguanidine was started at once, within 8 hours the baby's temperature was normal, and within 24 hours marked improvement in his general condition was evident.

He passed no stools on the second and third days of treatment, and thereafter had no more than two stools formed daily. Sulfanilylguanidine was discontinued after 4 days. The child was discharged on the 12th day.

85734, male, colored, aged 12 months. Admitted on first day of illness. Chief symptoms: fever, diarrhea. He had passed 8 stools in the 12 hours before entry. His admission temperature was 39.5°C. (103°F.) and his white blood cell count 7500. He was seriously ill, and moderately dehydrated. His stools contained pus, but no blood, and yielded on culture the Sonné type of dysentery organism. During the first 18 hours in the hospital the baby was starved and given parenteral fluids. On the second day, sulfanilylguanidine was begun. The temperature which was already tending downward was normal within 28 hours after chemotherapy was instituted, and within 36 hours there was marked improvement in the child's general condition. The stools remained watery for 24 hours after the drug was begun, but diminished in number and become semiformed on the second day; after the third day they were pasty and no more than three in number daily. Sulfanilylguanidine was continued for a week. The baby seemed quite well after the first few days in the hospital and was discharged after 14 days.

A-16296, female, colored, aged 5 years. Admitted on first day of illness. Chief symptoms: high fever, severe diarrhea. Her temperature was reported to have been above 106° before admission, and 15 stools containing blood and pus to have been passed in 10 hours. At the time of entry she was extremely ill, delirious, and drowsy, with a temperature of 40.5°C. (105°F.), and a white blood cell count of 10,500. Soon after admission her temperature rose to 41.4°C. (106.5°F.) and she had two convulsions. Stool culture revealed the Flexner type of dysentery organism. The child was treated with parenteral fluids, and sulfanilylguanidine was begun on a 12-hour schedule sixteen hours after admission. Within 20 hours her temperature was normal, and her general condition greatly improved. She continued to have diarrheal stools in diminishing numbers during the next three days. They became pasty on the fourth day of treatment, but varied from 2–5 daily until the sixth day. Sulfanilylguanidine was stopped on the 12th day and the child went home after 14 days in the hospital.

A-16293, female, colored, aged 18 months. Admitted on second day of illness. Chief symptoms: fever, severe diarrhea. In the 24 hours before admission, she had passed 15 stools containing blood and pus. She was seriously ill on entry, with a temperature of 38°C. (100.4°F.), a white blood cell count of 11,100 and the Flexner type of dysentery organism was grown from her stools. Because of dehydration, a continuous intravenous drip was started immediately after admission. The following day her temperature remained above 39°C. and her diarrhea was severe, although the dehydration had been corrected. Treatment with sulfanilylguanidine on a 12-hour schedule was therefore begun, and within 24 hours the temperature was normal, and marked improvement in the general condition had

occurred. Frequent loose stools, many containing blood, continued for the next 5 days but steady improvement was evident in the character of the stools. By the 6th day of treatment, formed stools appeared, and after the 8th day, regular stool habits of 4 or less formed movements a day were established. Sulfanilylguanidine was discontinued after 10 days. The baby was discharged after 14 days in the hospital.

A-16689, male, colored, aged 2½ years. Admitted on second day of illness. Chief symptoms: fever, diarrhea, stomach ache. He was thought to have had a convulsion just prior to entry, and had passed 6 loose stools containing blood, pus and mucus in the 24 hours before admission. He was seriously ill, and moderately dehydrated when first seen, his admission temperature of 39°C. (102.2°F.) soon rising to 40.1° (104.1°). His white blood cells numbered 4150 and the Flexner type of dysentery organism was isolated from one stool. Parenteral fluids were administered and sulfanilylguanidine begun. The temperature was normal the next day and the child seemed practically well. He passed only one stool (formed) that day, and thereafter his bowel movements numbered no more than two daily, and were of normal consistency. The drug was discontinued on the 6th day, and the boy went home in good condition after 11 days on the ward.

2. Treatment begun on or after the 4th day of disease

A-11197, male, colored, aged 24 months. Admitted on third day of illness. Chief symptoms: high fever, diarrhea. He had passed 15 stools in the 24 hours prior to admission. He was a malnourished, retarded child who had had severe diarrhea the preceding summer during which no pathogens were isolated from the stools, but following which he had developed agglutinins against S. paradysenteriae (Flexner Y) in a dilution of 1:160. He had been well in the interim. At the time of this second admission, he was emaciated, extremely dehydrated, and almost moribund. His temperature was 40.8°C. (105.5°F.) and his white blood cell count was 2500. His stools numbered 16 in the first 24 hours in the hospital, and although at first not of typical dysenteric character, subsequently showed blood and pus, and yielded on culture the Flexner type of dysentery organism. Fluid was given by continuous intravenous drip, and 12 hours after admission sulfanilylguanidine was started. His temperature varied between 37°C. and 39°C. for the next 3 days, and was thereafter normal. With the initial decrease in temperature 32 hours after the drug was started, the child appeared greatly improved clinically and his course from that point onward was favorable, although the stools were not completely normal until 12 days after admission. Sulfanilylguanidine was discontinued after 13 days. The child was kept on the ward 4½ weeks to be built up and was discharged in good condition.

A-17210, female, white, aged 10 months. Admitted on fourth day of illness. Chief symptoms: fever, diarrhea. On entry she was critically ill and markedly dehydrated. The temperature was 38.4°C. (101.1°F.) and the white blood cell

count was 5600. The stools were frequent and loose but contained no blood or pus, although the Flexner type of dysentery organism was cultured from them. A continuous intravenous drip was started immediately after admission and the dehydration was overcome, but the temperature remained elevated and the diarrhea continued with 6 to 12 stools daily. On the 6th day of the disease sulfanilylguanidine therapy was begun. Within 16 hours the temperature was normal and within 24 hours marked improvement in the general condition had occurred. The stools became formed within 36 hours and never thereafter exceeded 3 a day. The drug was stopped on the 7th day. The baby was discharged, after 13 days in the hospital, in excellent condition.

A-6340, male, white, aged 3 years. Admitted on seventh day of illness. Chief symptoms: vomiting, diarrhea, fever. On entry he was moderately ill and dehydrated with a temperature of 39.1°C. (102.3°F.) and a white blood cell count of 15,800. He was passing frequent watery stools containing blood, pus and mucus, from which the Flexner type of dysentery organism was isolated. Parenteral fluids were administered and sulfanilylguanidine was started at once. Within 36 hours his temperature was normal, the diarrhea began to check, and the boy appeared greatly improved. On the following day, he had two stools of normal consistency, and thereafter his course was uneventful. The drug was discontinued after the fifth day and the child went home in good condition after nine days in the hospital.

A-6830, female, colored, aged 28 months. Admitted on sixth day of illness. Chief symptoms: Fever, diarrhea, vomiting. She was admitted to the hospital moderately ill and dehydrated. The temperature was 38°C. (100.4°F.) the white blood cells numbered 30,800, and she was having frequent diarrheal stools containing blood and pus. Although her dehydration was corrected with parenteral fluids, the child remained sick, with a low grade fever and 12–13 stools daily. On the 7th day of the disease, treatment with sulfanilylguanidine was begun and within 8 hours the temperature had dropped to normal and remained so. Stools diminished in number and became partly formed, but continued to be abnormal both in frequency and character. After seven days of therapy sulfanilylguanidine was stopped. In another day or two the stools were of normal character and the child was discharged after 18 days in the hospital.

A-15141, female, colored, aged 6 months. Admitted on third day of illness. Chief symptoms: fever, diarrhea, vomiting. On entry she was severely ill and moderately dehydrated. Her temperature was 40.1°C. (104.1°F.) and white blood cell count was 16,100. The stools were loose, not at all dysenteric in appearance, but the Flexner type of dysentery organism was grown from them. Following a period of starvation and parenteral fluids, she was given increasing feedings but continued to have fever and 6–12 stools daily. On the 6th hospital day, the 8th day of her illness, the temperature reached 41.4°C. (106.5°F.) and the baby was desperately

ill. She was semistuporous and had frequent twitching of the extremities. It was felt that she would probably not survive. Sulfanilylguanidine was started at this point. The baby remained severely ill for several days, requiring parenteral fluids, but the temperature began a slow downward course within a few hours after the drug was started and reached normal 8 days later. The diarrhea did not abate for several days and the stools did not become normal until the 11th day of sulfanilylguanidine therapy. The child's general condition improved only slowly. During the second week of sulfanilylguanidine therapy there was an unexplained rise in temperature to 38.6°C. (101.4°F.) over a 2 day period, not associated with diarrhea. Sulfanilylguanidine was continued for 19 days in this case. The child finally made a complete recovery and was discharged in excellent condition after 4½ weeks in the hospital.

A-16338, male, colored, aged 8 months. Admitted on fifth day of illness. Chief symptoms: vomiting, ear ache, diarrhea. This baby had been followed in the dispensary because of vomiting associated with mild catarrhal otitis media. On the 4th day of illness diarrhea developed and on the following day the baby became prostrated and dehydrated. On entry, his temperature was normal but shortly rose to 39.4°C. (102.9°F.) and he was moderately ill. The white blood cell count was 11,700. After 3 days of irregular fever and frequent loose bowel movements, blood and pus suddenly appeared in the stools, and the laboratory reported the isolation of the Sonné type of dysentery organism from the original stool cultures. It was difficult to keep the baby hydrated despite liberal amounts of fluids given parenterally. On the 9th day of his illness, sulfanilylguanidine was started. The temperature was normal within 24 hours and the number of stools lessened. But the child remained ill for several days, and the stools did not become normal until the 10th day of treatment. Sulfanilylguanidine was discontinued after 12 days. The baby was sent home in good condition after 3 weeks on the ward.

A-14616, female, white, aged 11 months. Admitted on the seventh day of illness. Chief symptoms: fever, diarrhea, vomiting. She was extremely ill, moderately dehydrated. Shortly after admission her temperature rose to 41.2°C. (106.1°F.). The white blood cells numbered 23,000. Her frequent stools showed blood and pus, and the Flexner type of dysentery organism was isolated from them. Despite abundant parenteral fluids and the usual supportive management, she showed no improvement by the 3rd hospital day and sulfanilylguanidine therapy was begun. A decrease in the number of stools was apparent at once following the institution of chemotherapy, but no change in the temperature or the general condition occurred. The temperature gradually fell, reaching normal on the 6th day of drug therapy, and the stools finally became normal on the 9th day. The drug was stopped after 11 days, and the child was dismissed in good condition after 19 days on the ward.

99513, male, colored, aged 4 years. Admitted on the seventh day of illness. Chief symptoms: fever, stomach ache and diarrhea. On admission he was moderately ill

with a temperature of 39°C. (102.2°F.), the white blood cell count was 8200, and the stool cultures positive for the Flexner type of dysentery organism. Diarrhea and irregular fever continued, and on the 10th day of the disease sulfanilylguanidine was begun and given for 6½ days. His temperature became normal within 8 hours after the drug was started and remained so. Stools did not become normal until the 4th day of drug therapy, the 14th day of illness. The child was sent home in good condition after 13 days on the ward.

A-14242, male, colored, aged 13 months. Admitted at the end of the first day of illness. Chief symptoms: fever, diarrhea. On admission he was moderately ill with a temperature of 40.4°C. (104.7°F.) and the white blood cells numbered 13,600. The stools were numerous, contained blood, pus and mucus, and on culture yielded the Flexner type of dysentery organism. His temperature gradually dropped to normal 24 hours after entry and his general condition improved. The passage of five to eight dysenteric stools continued daily. A low grade fever (38.2°) returned for several days in the second week and on the 12th day of his disease sulfanilylguanidine was started. The temperature and stools became normal the day after drug therapy was begun and remained so. Sulfanilylguanidine was administered for 3 days, and the child went home well after 18 days in the hospital.

A-17555, female, colored, aged 8 months. Admitted two weeks after onset of illness. Chief symptoms: diarrhea, fever, vomiting. She was critically ill and badly dehydrated on entry. Temperature was 39°C. (102.2°F.) and white blood cells numbered 12,800. The bowel movements were frequent, showed mucus and pus, and yielded the Flexner type of dysentery organism on culture. Although the dehydration had been overcome by means of a continuous intravenous drip, the diarrhea and fever persisted, and 36 hours after admission sulfanilylguanidine was started. The temperature fell to normal 20 hours after the drug was begun, but it subsequently rose on two occasions to 38.4°C. and 39°C. Normal temperature was not established until after 5 days of chemotherapy, and stools did not become completely normal for 3 weeks, although improvement was apparent after one week. The drug was continued for 2 weeks and the baby gradually improved. She was retained on the ward for more than a month to improve her nutrition and overcome a thrombophlebitis due to the continuous intravenous drip.

REFERENCES

(1) MARSHALL, BRATTON, WHITE AND LITCHFIELD: Sulfanilylguanidine: a chemotherapeutic agent for intestinal infections. *Bull. Johns Hopkins Hospital*, **67**: 163–188, 1940.

(2) BRATTON AND MARSHALL: A new coupling component for sulfanilamide determination. *Jour. Biol. Chem.*, **128**: 537, 1939.

(3) LONG, HAVILAND, EDWARDS AND BLISS: The toxic manifestations of sulfanilamide and its derivatives. *Jour. Am. Med. Ass.*, **115**: 364, 1940.

PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in the Hurd Memorial Hall, November 11, 1940

The President of the Society, Dr. Warfield M. Firor, presided. Abstracts of the papers and discussions follow:

Case Presentation: Weil's Disease. By H. P. Goldberg and E. D. Davens. (Department of Pediatrics.)

Two cases of Weil's Disease in children were reported. One child's illness corresponded exactly to the classical jaundiced form. The other showed no jaundice, but presented evidence of severe generalized infection. Both had cerebrospinal fluid pleocytosis but meningeal signs were present only in the jaundiced case. Renal changes, as evidenced by hematuria, albuminuria, and the presence of casts, were found in both. The child with jaundice had increased bile and urobilin in the urine, an elevated direct Van den Bergh, and nitrogen retention. The children made good recoveries. The leptospiral etiology of the illness was proved by guinea pig inoculation of urinary sediment and by demonstration of agglutination titres of 1:30,000 on the 28th day of the illness in each case. Epidemiological studies by Dr. Thomas Ward indicated that a well was the probable source of infection.

Attention was directed to the difficulties in diagnosis of the non-jaundiced cases which often showed mild grippe-like symptoms or only evidence of meningeal involvement. Approximately 50 per cent of leptospiral infections show no jaundice.

DISCUSSION

Dr. E. A. Park said that these were the first two cases of Weil's Disease that he had seen in the Harriet Lane Home. This is one more disease in which high fever and meningeal symptoms are associated with changes in the spinal fluid. If jaundice does not occur Weil's Disease is likely not to be thought of. The recognition of these cases has served to put us on guard.

Dr. Goldberg and Dr. Davens made the presentation, so were prevented from saying that they were responsible for the correct diagnosis.

A Method for the Study of Neuromuscular Transmission in Human Subjects. By A. M. Harvey and R. L. Masland.

(For complete paper see page 81.)

DISCUSSION

Dr. Howard J. Curtis said that Dr. Harvey's experiments dealt with one of the most controversial subjects in neuromuscular physiology. He said that any information on this subject was welcome. The reason for the controversy was that the techniques involved are difficult in animal experimentation and when applied to human experimentation, they are even more difficult. Dr. Curtis complimented Dr. Harvey for undertaking this problem and said that the results were extremely interesting and showed great promise. As Dr. Harvey had indicated, however, the results reported were of a preliminary nature, and one should be cautioned against expecting this method to be useful as a clinical tool until after more extensive measurements had been made.

Peritoneoscopy. By R. T. SHACKELFORD. (Department of Surgery.)

Doctor B. M. Bernheim introduced peritoneoscopy to America at the Johns Hopkins Hospital in 1911 but the procedure was abandoned after its successful use on two cases. J. C. Ruddock revised and improved upon the method and has been the chief cause of its present popularity. Since 1938 we have used Ruddock's instrument and technique on 81 cases with encouraging success. In this group there was no mortality and only one complication which, however, was followed by an uneventful convalescence. There have been three failures to make a satisfactory examination and two instances in which an incorrect diagnosis was made.

Peritoneoscopy should not be used in cases with acute inflammatory conditions of the abdomen, abdominal distention, and in those in which massive abdominal adhesions are present. It should be used only with a specific purpose in mind such as to make a differential diagnosis, confirm a clinical impression or define and localize a tumor and then only after simpler measures have been unsuccessful in establishing the diagnosis. We have found it most useful in the diagnosis of lesions of the liver and female pelvic organs, in tuberculous peritonitis and in determining the operability of carcinoma of the stomach.

With these limitations in mind we believe that it is a safe and useful diagnostic procedure in a small group of carefully selected cases.

Immunological Studies on the Natural Sensitization of Man. By ROBERT A. COOKE. (New York.)

The term *natural sensitization* as applied to man is used merely to indicate the fact that certain allergies appear as the result of sensitizations to substances with which we have normal natural contacts. They are not purposely induced as the result of parenteral injections. In this concept of the term, we do not state nor do we deny that the mechanism of sensitization may arise *de novo* from forces that we know not of, and other than the ordinary immunological ones.

In these serological studies by my associates and myself the past few years, we have made use of the Prausnitz Küstner phenomenon of passive transfer of

sensitiveness in two ways. We have injected serial dilutions of sensitive serum into sites in the skin of normal test-subjects. These sites are tested 48 hours later with antigen. This, we speak of as the dilution test to determine the amount and probably also the activity of the skin sensitizing antibody in the serum. One-tenth of a ml. of some sera diluted several thousand times will still give positive reactions. Another method is the neutralization test in which sensitive serum is mixed with graduated amounts of antigen and the mixtures injected as sites in normal test-subjects. Forty-eight hours later these sites are retested with the antigen to determine whether the antibody has been used up in whole or in part.

Reactions to many antigens are frequently encountered in the serum of a naturally sensitive man. Our studies make it seem probable that these multiple reactions are due to a single antibody since one antigen may effect neutralization against many other antigens, even those biologically unrelated, and when serum antibody is increased in amount as it usually is after specific injection there is also a proportional increase in the antibody reacting with other antigens and even those not subject to cross neutralization. The dominant antigen however, is dominant only in reference to a special serum and is related to clinical sensitiveness, but no antigen is inherently dominant nor is there any constant relation between antigens. Furthermore, the antibody in any particular serum, when studied in detail with regard to its reactions and neutralizations, has what approaches a finger-print individuality. This fact, plus the evident lack of specificity of the skin sensitizing antibody, is at variance with the specific results obtained in studies on artificially induced antibodies and makes us question the classical concept of the immunologically induced origin of this antibody in the naturally sensitive man.

In our serum studies of autumnal hay fever patients after injections with ragweed extracts, we encountered what appears to be a new antibody, which on account of its action we termed a blocking antibody, which is induced by injection and is strictly specific. It appears to bind antigen, but without determinable precipitation, and thus relates itself to the so-called soluble precipitins of Pappenheimer, Heidelberger and others. It differs from the skin sensitizing antibody also in that it is heat stable, readily filters through the placenta and may be produced in normal subjects without the concomitant appearance of a skin reacting substance. It seems, therefore, to be entirely distinct from the skin sensitizing antibody. Evidence has also been obtained which indicates that this inhibiting antibody is not the entire, if it is any, factor in clinical immunity in hay fever.

DISCUSSION

Dr. Leslie N. Gay said it was a pleasure to welcome Dr. Cooke to the meeting of the Johns Hopkins Medical Society. For many years he has directed his attention to the solution of the problems pertaining to allergic diseases and his scientific progress in his research has been a great stimulation to those of us who are also interested in this subject.

Experiments pertaining to this "blocking antibody" have been carried on by Doctors Eagle and Winkenwerder in this clinic. Unfortunately using the same technique they have not been able to confirm Dr. Cooke's work in every instance and consequently they have raised a reasonable doubt as to its importance. At the same time, they have been unable to explain their discrepancies. If there is a new antibody created by the methods of treatment which we have adopted in the care of patients suffering with hay-fever, it is thus far only of academic interest as the successful clinical results which are obtained by the specific treatment are not in any way dependent upon its presence or absence in the post-treated serum.

If Dr. Cooke has found a serological method which will differentiate patients who will have constitutional reactions at a fixed point in their treatment schedule from those who will not have reactions no matter what the dose might be, it will be a discovery of great clinical value. For these serious reactions occur without warning and often without any logical reason.

The further development of this phase of Dr. Cooke's work will be looked forward to with the greatest interest.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarialy those of the members of the Editorial Board of this Journal.)

Essentials of the Diagnostic Examination. By JOHN B. YOUMANS. 417 pp. Illus. $3.00. *The Commonwealth Fund, New York, and Oxford University Press, Humphrey Milford, London, 1940.*

This compact little handbook on the essentials of the diagnostic examination has many qualities to recommend it. The material is well organized, clearly and simply expressed. Part I presents the fundamentals of history-taking and the physical examination; Part II is devoted to the more important clinical laboratory tests. Among the latter are included the accepted methods for the determination of sulfanilamide and sulfapyridine in the blood. The text is supplemented with a number of useful tables and diagrams, and there is an excellent list of selected references in addition to a carefully arranged index at the end of the book.

This book owes its compactness to the skillful condensation of the subject matter and to the excellent grade of thin paper on which it is published. The print is sufficiently large to be easily legible. The color plates illustrating the section on hemotology are somewhat diagrammatic, but serve their purpose in a book of this type.

Dr. Youmans has made a real contribution in preparing this manual. It should prove extremely valuable to the medical student, the laboratory worker, and the practicing physician.

W. H. B.

Diseases of the Digestive System and Food Allergy. By JOSEF S. SMUL. 219 pp. $3.50. *Medical Library Company, New York, 1940.*

The author has published this volume, especially, to express his personal views on the relationship of allergy to disturbances of the gastro-intestinal tract. After many years of clinical observation the conclusion has been reached that allergy to food causes not only the many bizarre symptoms usually considered as functional in origin but also such organic conditions as gastro-duodenal ulcer, ulcerative colitis, cholangitis, cirrhosis, acute yellow atrophy of the liver, and many others. Such claims are of course hypothetical, since immunologic proof of an allergic basis of these conditions has never been obtained. The volume adds nothing to current knowledge of gastro-intestinal diseases.

W. L. W.

The Chinese Way in Medicine. By EDWARD H. HUME. 189 pp. Illus. $2.25. *The Johns Hopkins Press, Baltimore, 1940.*

This book contains three lectures on the history of Chinese medicine. The

first lecture on the Universe and Man in Chinese medicine describes the philosophic and religious concepts on which Chinese medicine is based. Although the legendary history of China reaches back to about 3,000 years B.C., its authentic history dates from the eighteenth century B.C., while it becomes quite clear during the Chou Dynasty (1122–249 B.C.), when much of the permanent philosophy of China was developed. The influence of and the commentaries on this philosophy, as bearing on medical ideas and practice, is the main theme of this lecture.

In the second lecture, brief accounts of the great men of Chinese medicine are presented, beginning with the three legendary emperors popularly known as the founders of medicine. The second of these is Shên Nung who lived, according to the legend, from 2838 to 2698 B.C., and having introduced herbs as remedies, is known as the ancient god of medicine and agriculture.

The third lecture gives an account of some distinctive contributions of Chinese medicine and describes some of the present customs of the Chinese doctors of the old school.

It is difficult to compare Chinese medicine with that of the Western world, as its origins and its concepts differ so widely from ours. Progress as we have seen it has not gone on in China, and science in the Western sense has not existed. The fundamental break with the past that has been necessary in the introduction of Western medicine into China can be appreciated by reading these lectures by Dr. Hume. Many interesting examples of Chinese philosophy and folk-lore are presented.

G. C. R.

The Kosher Code of the Orthodox Jew. By S. I. Levin and Edward A. Boyden. 243 pp. $4.50. *University of Minnesota Press, Minneapolis, Minn. 1940.*

"And ye shall be holy men unto me: neither shall ye eat any flesh that is torn of beasts in the field; ye shall cast it to the dogs." This passage in *Exodus 22:31* constitutes the legal basis of the orthodox Jews' elaborate code of ritual slaughtering. With the passage of time and the accumulation of custom the ritual came to include two parts,—a prescribed method of slaughtering based upon severing the vessels of the neck, and an inspection of the carcass as to its suitability for food according to ritual prescription. The developing practice in these two respects in the Palestinian community was first compiled in the Mishna in the third century of the common era. Comment, exposition and adjudication of the rabbinical courts during the next four centuries were finally compiled in the Gemara. Mishna and Gemara together constitute the Talmud.

During the succeeding centuries commentaries, compilations, codifications and adjudications have been issued by various rabbis and rabbinical tribunals. They are of varying authority. Altogether this constitutes a literature not less voluminous than that to be found in the records of the United States Supreme Court in respect to one of the lesser clauses of the Constitution.

In actual operation the ritual has provided for the inspection of untold millions of carcasses, and while the attitude of this inspection has been legalistic rather than scientific, inevitably the results of the observations have penetrated into the

fabric of the ritual. It was the interest of Professor Boyden to discover the extent and character of these anatomic observations that led him to collaborate with Rabbi Levin in the publication of this book,—a translation of those sections of the Talmud and of the chief commentaries dealing with the laws of Terefah. Professor Boyden's comments in respect to the anatomical significance of various passages are entertainingly sandwiched between those of the rabbinical commentators of a thousand years ago.

Since the biblical injunction against "Terefah" means literally "torn of beasts" the early development of the law entailed extension of the injunction to include under "Terefah" animals whose viscera showed puncture wounds such as might have been caused by the teeth or claws of an attacking animal. The gradual extension of this conception to include bronchiectasis, pulmonary abscesses and other diseases involves a progressive development of legal fictions. The student of social problems can rarely have an opportunity to examine the progressive development of legal fictions and the adaptation of a primitive injunction to the changing circumstances of civilized organization in a more explicit fashion and over a longer period of time than in the source material here laid bare.

J. S. F.

The Emperor's Itch: The Legend concerning Napoleon's Affliction with Scabies. By REUBEN FRIEDMAN. 82 pp. Illus. $1.50. *Froben Press, New York, 1940.*

For those who enjoy the historical aspects of medicine, this contribution holds considerable interest and much information. There are four chapters: *Legend*, *Discussion*, *Summary*, and *Conclusion*.

The legend deals with the Napoleonic "pose," referring of course to the hand held within the partially open coat, supposedly because of continual itching. This is illustrated in reproductions of paintings and of sculpture. The author then discusses the question of the Emperor's supposed infestation with scabies which was almost epidemic in the European armies of this period. Napoleon's disease has been ascribed to a dramatic incident during the siege of Toulon in 1793. On the death of a gunner (known to have scabies), Napoleon, it was told, manned a cannon, handling the ramrod, and thus contracted scabies.

The authenticity of this legend of infestation is discussed in detail and most critically. In the summary, the author, in a convincing manner, repudiates this diagnosis. However, he suggests another possible diagnosis, namely, *dermatitis herpetiformis*, a rare disease indeed; and as a secondary compromise, he suggests *neurotic excoriations*. In this respect, unfortunately, he does not substantiate his convictions, because there are no criteria whereby the author's suspicion can be correctly determined.

This little essay is, evidently, the outcome of considerable research. It is admirably presented together with excellent illustrations; and it is concluded with a quoted brief, amusing chapter on "The Itch." All these features recommend the book for the enjoyment of reading.

I. R. P.